26 April 2023
EMA/214413/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cosentyx

International non-proprietary name: secukinumab

Procedure No. EMEA/H/C/003729/II/0090

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AIN457	Secukinumab
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AN	Abscesses and inflammatory nodules
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
AST	Aspartate aminotransferase
BCC	Basal cell carcinoma
BDR	Bioanalytical data report
BMI	Body mass index
CMQ	Customized MedDRA query
COVID-19	Coronavirus Disease 2019
CRF	Case record form
hsCRP	High sensitivity C-Reactive Protein
CSR	Clinical study report
CTCAE	Common toxicity criteria adverse event
DLQI	Dermatology Life Quality Index
EAIR	Exposure-adjusted Incidence rate
EOT	End of treatment
EQ-5D-3L	Euro-QoL 5-Dimension 3-level Health Status Questionnaire
ESR	Erythrocyte sedimentation rate
EX	Exposure in 100 subject-years
FAS	Full analysis set
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
HGB	Haemoglobin
HIV	Human immunodeficiency virus
HLGT	High level group term
HLT	High level term
HiSCR	Hidradenitis Suppurativa Clinical Response
HS	Hidradenitis suppurativa
HS-PGA	Hidradenitis Suppurativa Physician's Global Assessment
IBD	Inflammatory bowel disease
ICE	Intercurrent event
IgG1	Immunoglobulin G1
IL-17A	Interleukin-17A
IR	Incidence rate
IRT	Interactive Response Technology

LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LoE	Lack of efficacy
LPLV	Last patient last visit
LS	Least squares
MACE	Major adverse cardiovascular events
MAH	Marketing Authorisation Holder
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MELRM	Mixed effects logistic regression model
MI	Myocardial Infarction
mHSS	Modified Hidradenitis Suppurativa Score
MMRM	Mixed model for repeated measures
NASH	Non-alcoholic steatohepatitis
NMQ	Novartis MedDRA Query
NRS	Numerical Rating Scale
NSCLC	Non-small cell lung cancer
HS-PGA	Hidradenitis suppurativa physician's global assessment scale
PGI-c	Patient Global Impression of change
PGI-s	Patient Global Impression of severity
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
PsO	Psoriasis
PSUR	Periodic safety update report
PT	Preferred term
Q2W	Once every two weeks
Q4W	Once every four weeks
QFT	QuantiFERON® TB-Gold test
QoL	Quality of life
RAS	Randomised analysis set
RMP	Risk management Plan
RSI	Request for Supplemental Information
SA	Scientific Advice
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-Cov-2	Severe acute respiratory syndrome coronavirus 2
s.c.	Subcutaneous
SCC	Skin squamous cell carcinoma
SD	Standard deviation
SE	Standard error
SIB	Suicidal ideation and behaviour
SMQ	Standard MedDRA query
SOC	System organ class

SY	Subject year
TBL	Total bilirubin
TE-ADA	Treatment-emergent anti-drug-antibodies
TNF-α	Tumour necrosis factor-α
ULN	Upper limit of normal
VAS	Visual analogue scale
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 30 May 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of Hidradenitis Suppurativa (HS) for COSENTYX, based on interim results from two Phase III studies CAIN457M2301 (SUNSHINE) and CAIN457M2302 (SUNRISE); These studies are ongoing, multi-center, randomized, double-blind, placebo-controlled, parallel group Phase 3 studies conducted to assess the short (16 weeks) and long-term (up to 52 weeks) efficacy and safety of two secukinumab dose regimens (Q2W or Q4W) compared to placebo in adult subjects with moderate to severe HS; As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2. of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0144/2019 on the granting of a (product-specific) waiver for secukinumab in the treatment of hidradenitis suppurativa.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP in October 2017 (EMEA/H/SA/1281/4/2017/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola

Timetable	Actual dates
Submission date	30 May 2022
Start of procedure:	18 June 2022
CHMP Rapporteur Assessment Report	12 August 2022
PRAC Rapporteur Assessment Report	18 August 2022
PRAC Outcome	01 September 2022
CHMP members comments	05 September 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	08 September 2022
Request for supplementary information (RSI)	15 September 2022
CHMP Rapporteur Assessment Report	15 November 2022
PRAC Rapporteur Assessment Report	18 November 2022
PRAC Outcome	01 December 2022
CHMP members comments	05 December 2022
Updated CHMP Rapporteur Assessment Report	08 December 2022
2nd Request for supplementary information (RSI)	15 December 2022
CHMP Rapporteur Assessment Report	06 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur Assessment Report	23 March 2023
3rd Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	12 April 2023
CHMP members comments	17 April 2023
Updated CHMP Rapporteur Assessment Report	20 April 2023
Opinion	26 April 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Hidradenitis suppurativa (HS), also called 'acne inversa' or 'maladie de Verneuil,' is a painful, chronic, recurrent and debilitating inflammatory skin condition of the pilosebaceous follicle with an underlying immune system imbalance that occurs in genetically predisposed individuals.

The therapeutic indication initially claimed by the MAH was:

Cosentyx is indicated for the treatment of moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy.

The initially proposed dose regimen was:

The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by a maintenance dose of 300 mg every 2 weeks. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.

Epidemiology and risk factors

Although epidemiological prevalence estimates vary widely (0.03% to 4.0%) and geographical differences exist, a prevalence of approximately 0.1% to 1% is accepted by the scientific community. The disease starts after puberty, and women are more frequently affected than men in a ratio of 3:1. Risk factors include obesity and smoking.

Clinical presentation

HS typically presents with painful, deep, inflammatory lesions, mostly inflammatory nodules and abscesses, which progressively scar and suppurate and lead to malodorous discharge in the apocrine gland-bearing parts of the body. Inflammatory lesions are complicated during disease progression by sinus tract formation and fistulisation and may lead to hypertrophic scarring with a possible impact on function. The most common areas affected are the axillae, the groin and the anogenital region. HS has a highly negative impact on QoL and devastating psychological effects, with an impact greater than for many other dermatologic diseases. Patients with HS also often suffer from depression, social isolation, impaired sexual health and difficulty performing work duties.

Management

European treatment guidelines for HS were developed in 2015, followed by North American clinical management guidelines in 2019. These guidelines recommend a variety of medical treatments that can be used to manage the disease, including topical and systemic antibiotics, hormonal therapies, retinoids, systemic immunomodulators and biologics. Recurrent combination therapy using multiple antimicrobials represents the first step to control the symptoms in patients with HS. However, it is recognised that HS is not an infectious disease, but rather a chronic inflammatory condition, with elevated systemic levels of

inflammatory markers. Therefore, systemic anti-inflammatory agents could be considered a more appropriate therapeutic strategy than antibiotics. Once irreversible fibrosis occurs, medical treatment can only control some symptoms, while the only option to manage fibrotic lesions is surgery. Currently, adalimumab (Humira), an anti-TNF-α antibody, is the only biological therapy approved for the treatment of adults with moderate to severe HS (approval granted in 2015 in the US and EU). Two similarly designed Phase 3 studies demonstrated the superiority of weekly adalimumab over placebo with respect to Hidradenitis Suppurativa Clinical Response (HiSCR) rate at Week 12: 41.8% adalimumab vs. 26.0% placebo in PIONEER I, and 58.9% adalimumab vs. 27.6% placebo in PIONEER II. However, considering the very limited treatment armamentarium, an unmet need exists for additional systemic therapies.

2.1.2. About the product

Secukinumab (AIN457, Cosentyx) is a recombinant, fully human monoclonal anti-human interleukin (IL)-17A antibody of the IgG1/κ-class. Secukinumab binds to human IL-17A and neutralises the bioactivity of this proinflammatory cytokine. Secukinumab (Cosentyx) was initially authorised in the EU on 15 Jan 2015 for the treatment of plaque psoriasis (PsO) in adult patients. New indications for psoriatic arthritis (PsA), ankylosing spondylitis (AS) in adult patients, non-radiographic axial spondyloarthritis (nr-axSpA;), PsO in children and adolescents from the age of 6 years, and the juvenile idiopathic arthritis (JIA) categories of enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA) in children and adolescents from the age of 6 years) were authorised. According to the MAH, secukinumab is currently authorised in over 100 countries worldwide.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific Advice related to the following aspects of the proposed clinical programme was provided by the CHMP in October 2017 (Procedure No.: EMEA/H/SA/1281/4/2017/II):

- Proposed patient population
- Primary and secondary endpoints
- Study design
- Size of safety database
- Overall sufficiency of proposed programme.

The MAH has generally followed recommendations provided in the Scientific Advice. Compliance and deviations from the scientific advice are discussed in relevant sections of the report.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has also provided a statement confirming that all clinical trials conducted outside of the European Union meet the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

According to the current CHMP guideline on environmental risk assessment (CHMP/SWP/4447/00 corr 2), for products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment. As a monoclonal antibody, secukinumab falls within the scope of this provision. The MAH's ERA, providing a justification for not performing a detailed environmental risk assessment for secukinumab, is thereby considered acceptable.

2.2.2. Conclusion on the non-clinical aspects

From the non-clinical point of view, the extension of indication application is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: CAIN457M2301 Wk 16 **Countries:** Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Hungary, India, Israel, Italy, Japan, Mexico, Philippines, Poland, Portugal, Republic of Korea, Russia, Slovakia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States **Start:** 31-Jan-2019 **End:** Ongoing	**Design, purpose & population:** A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNSHINE)	**Total:** 541 **Age:** 18-73 (36.1) years **Groups:** 4 (1:1:0.5:0.5) 181 180 180 (both placebo groups combined)	**Form(s):** Secukinumab 300 mg/2 mL PFS Placebo PFS matching Secukinumab 300 mg/2 mL **Duration:** 52 weeks Treatment period 1 (16 weeks) Treatment period 2 (36 weeks) **Doses:** AIN457 300 mg every 2 weeks AIN457 300 mg every 4 weeks Matching Placebo every 2 or 4 weeks **Regimen and route:** AIN457 SC injection at randomization, week 1, 2, 3, 4 and then every 2 weeks up to week 48 (Q2W) or 4 weeks up to week 48 (Q4W) Matching placebo SC injection at randomization week 1, 2, 3, 4 and then every 2 or 4 weeks up to week 16, then randomized to respective AIN457 groups Q2W or Q4W	**Study Status:** Enrollment complete, study ongoing **Report no.:** [CAIN457M2301] Wk 16 **Cut-off:** 01-Oct-2021 **Report Date:** 14-Apr-2022 **Other reports:** [DMPK RCAIN457M2301-int-ig] [DMPK RCAIN457M2301-int-pk] [DMPK RCAIN457M2301-int-ig nab] [DMPK RCAIN457M2301-pk-Clinical Study]

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: CAIN457M2302 Wk 16 **Countries:** Argentina, Belgium, Bulgaria, Canada, Colombia, Croatia, Czech Republic, Denmark, France, Germany, Greece, Guatemala, Hungary, India, Israel, Italy, Lebanon, Lithuania, Malaysia, Netherlands, Philippines, Poland, Russia, Singapore, Slovakia, South Africa, Spain, Switzerland, Turkey, United Kingdom, United States, Vietnam **Start:** 25-Feb-2019 **End:** Ongoing	**Design, purpose & population:** A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNRISE)	**Total:** 543 **Age:** 18-71 (36.3) **Groups:** 4 (1:1:0.5:0.5) 180 180 183 (both placebo groups combined)	**Form(s):** Secukinumab 300 mg/2 mL PFS Placebo PFS matching Secukinumab 300 mg/2 mL **Duration:** 52 weeks Treatment period 1: 16 weeks Treatment period 2: 36 weeks **Doses:** AIN457 300mg Q2W AIN457 300 mg Q4W Matching Placebo Q2W or Q4W (combined) **Regimen and route:** AIN457 SC injection at randomization, week 1, 2, 3, 4 and then every 2 weeks up to week 48 (Q2W) or 4 weeks up to week 48 (Q4W) Matching placebo SC injection at randomization week 1, 2, 3, 4 and then every 2 or 4 weeks up to week 16 then randomized to respective AIN457 groups Q2W or Q4W)	**Study Status:** Enrollment complete, study ongoing **Report no.:** [CAIN457M2302] Wk 16 **Cut-off Date:** 23-Sep-2021 **Report Date:** 07-Apr-2022 **Other reports:** [DMPK RCAIN457M2302-int-ig] [DMPK RCAIN457M2302-int-pk] [DMPK RCAIN457M2302-iga-int]

2.3.2. Pharmacokinetics

Pharmacokinetics of secukinumab in hidradenitis suppurativa (HS) patients was investigated after treatment of secukinumab 300 mg s.c. every two weeks (Q2W) or every four weeks (Q4W). Blood samples were collected pre-dose for pharmacokinetic (PK) analysis at the scheduled visits (pre-dose at baseline, week 16, week 24, week 52, week 60). Secukinumab concentrations were listed by treatment and subject and Cmin were determined. Descriptive summary statistics were reported. An ELISA method was used for the bioanalytical analysis of secukinumab in serum, with a lower limit of quantification (LLOQ) of 160 ng/ml.

Steady state levels were observed for both the Q2W and Q4W groups at Weeks 24 and 52 for subjects

who started secukinumab treatment at the beginning of the study (**Table 1**). The Q2W groups were already at steady state or close to steady state at Week 16 in studies M2301 and M2302. Steady state is reached at Week 24 in the Q4W groups. (**Figure 1**)

Subjects who switched from placebo to Q2W at Week 16 showed concentrations already close to steady state at Week 24, i.e., eight weeks after start of treatment. Subjects who switched from placebo to Q4W at Week 16 showed higher concentrations at Week 24 than later at steady state. (**Table 1**)

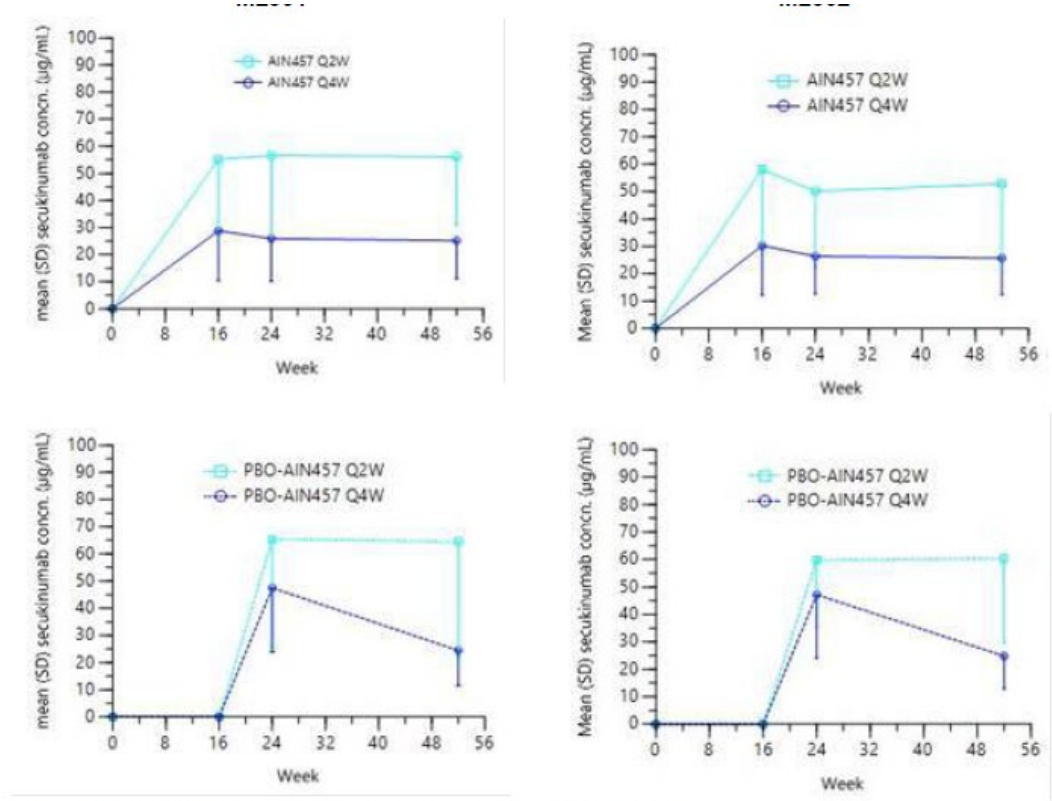
Table 1 Predose serum concentrations of secukinumab (µg/mL) (M2301 and M2302) (Full analysis set)

	M2301		M2302		M2301		M2302	
Visit	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
	300 mg Q2W				**300 mg Q4W**			
Week 16	142	55.1 (26.7)	152	58.1 (30.1)	152	28.8 (18.3)	153	30.2 (18.0)
Week 24	123	56.6 (29.6)	127	50.1 (27.8)	118	25.9 (15.8)	124	26.4 (13.8)
Week 52	70	56.0 (25.3)	83	52.8 (28.7)	71	25.2 (14.1)	76	25.7 (13.4)
	Placebo to 300 mg Q2W				**Placebo to 300 mg Q4W**			
Week 16	79	0.06 (0.382)	71	0.098 (0.745)	75	0 (0.0)	75	0.008 (0.067)
Week 24	65	65.3 (39.8)	59	59.8 (24.5)	61	47.4 (23.8)	62	47.2 (23.1)
Week 52	35	64.5 (42.5)	38	60.4 (30.8)	42	24.4 (12.9)	36	24.8 (12.0)

Source: [Study M2301-Table 14.2-15.1], [Study M2302-Table 14.2-15.1]

Observed serum exposure in HS subjects was lower than in other indications such as psoriasis (PsO).

Figure 1 PK trajectories (M2301 and M2302) (Full analysis set)



Source: [Study M2301-Table 14.2-15.1], [Study M2302-Table 14.2-15.1]

Population PK analysis

Population PK analysis was conducted on a pooled dataset comprising several PsO studies (A2102, A2103, A2211, A2212, A2220, A2302, A2303, A2308, A2310, A2311 and A2324) and the two pivotal HS Phase 3 studies M2301 and M2302.

A previously developed linear two-compartment model with first-order absorption for the subcutaneous (SC) administration and constant rate infusion for the intravenous (IV) administration was re–run on the present dataset and parameters were re-estimated. Covariates such as baseline body weight, population (paediatric versus adult), indication (HS versus PsO) and, in HS patients only – concomitant use of antibiotics, baseline disease severity (Hurley stage [I, II and III]) and baseline C-reactive protein (CRP) levels were evaluated to select a final population PK model. The full model with backward deletion approach was utilized for covariate modelling, and the backward deletion was performed at the p=0.001 significance level. A total of 20265 secukinumab concentrations (on average, 5 per subject) from 3787 PsO and HS patients were included in the population PK analysis. The parameter estimates of the final population PK model are presented in **Table 2**.

Table 2 Parameter Estimates of Final Population PK Model

Parameter	NONMEM Estimates			
[Units]	**Point Estimate**	**%RSE**	**95% CI**	
CL PsO [L/day]	0.198	1.85	0.191-0.205	
V_c [L]	3.78	2.20	3.62-3.94	
Q [L/day]	0.345	4.75	0.313-0.377	
V_p [L]	2.82	2.99	2.65-2.99	
KA [1/day]	0.174	2.98	0.164-0.184	
F1 adults	0.735	1.73	0.71-0.76	
CL~Weight	0.882	2.30	0.842-0.922	
V_c~Weight	0.784	7.14	0.674-0.894	
Q~Weight	0.804	19.0	0.504-1.1	
V_p~Weight	0.744	10.1	0.597-0.891	
F1 pediatrics	0.942	3.07	0.885-0.999	
CL HS (Baseline disease status Stage I&II) [L/day]	0.241	2.22	0.23-0.252	
CL HS (Baseline disease status Stage III) [L/day]	0.284	2.44	0.27-0.298	
CL HS~Baseline CRP	0.148	5.07	0.133-0.163	
Inter-individual				**CV%* or R**
ω^2_{CL}	0.101	2.63	0.0958-0.106	31.8
Covar η_{CL}, η_{Vc}	0.0576	7.43	0.0492-0.066	0.740
ω^2_{Vc}	0.0604	11.0	0.0474-0.0734	24.6
Covar η_{CL}, η_{Vp}	-0.0157	28.7	-0.0245--0.00688	-0.16
Covar η_{Vc}, η_{Vp}	0.022	22.7	0.0122-0.0318	0.28
ω^2_{Vp}	0.0997	6.33	0.0873-0.112	31.6
ω^2_{Ka}	0.12	10.8	0.0947-0.145	34.6
Residual variability				**CV%**
σ_{prop}	0.0402	0.63	0.0397-0.0407	20.0
σ_{add}	1170	18.8	739-1600	34.2

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = clearance, V_c = volume of central compartment, Q = inter-compartmental exchange flow rate, V_p = volume of peripheral compartment, KA= absorption rate constant, F1=bioavailability, σ_{prop} = proportional component of the residual error model, σ_{add} = additive component of the residual error model, 95% CI= 95% confidence interval on the parameter; R= correlation coefficient; ω^2_{CL}, ω^2_{Vc}, ω^2_{Q}, ω^2_{Vp} and ω^2_{KA} = variance of random effect of CL, V_c, Q, V_p and KA, respectively; Covar η_{CL}, η_{Vc} = covariance of random effect of CL and V_c; Covar η_{CL}, η_{Vp} = covariance of random effect of CL and V_p ; Covar η_{CL}, η_{Vc} = covariance of random effect of V_c and V_p ; SD=standard deviation of additive error (=$[\sigma^2_{add}]^{0.5}$)

The reference population is an 91 kg patient.

In the population PK analysis, it was found that

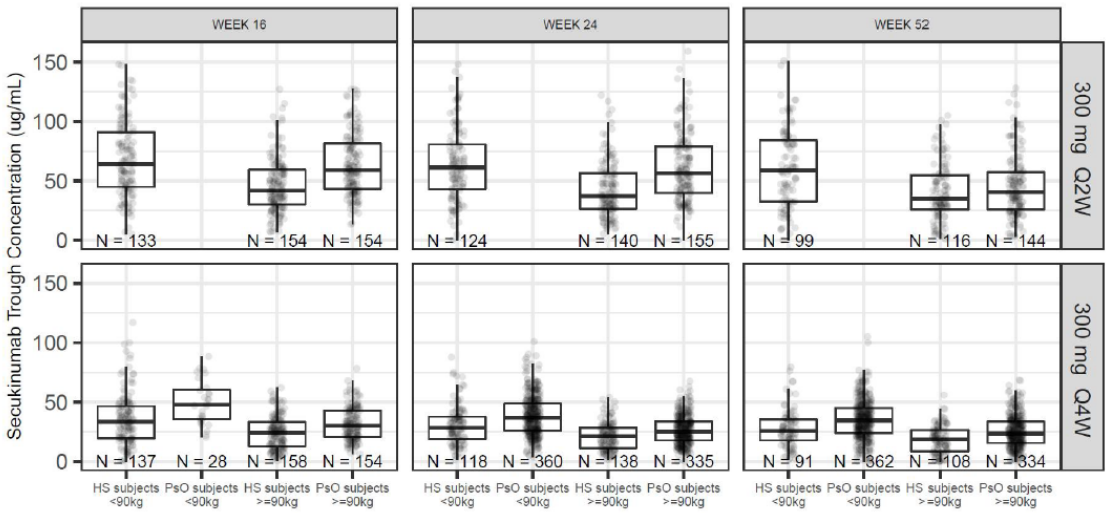
- Observed concentrations in HS subjects were lower when compared to PsO subjects (**Figure 2**). The population PK analysis estimated a 23% decrease in the average concentration at steady state (Cavg,ss) between HS and PsO subjects with the same bodyweight. This decreased drug exposure was attributed to an increase in clearance of 30% (0.257 L/d in HS compared to 0.198 L/d in PsO).
- No effect of concomitant use of antibiotics on drug exposure in HS subjects.

- The observed secukinumab concentrations for HS subjects with high hsCRP baseline value were lower compared to subjects with low hsCRP baseline value (**Figure 3**). The population PK analysis estimated the difference as 10% lower Cavg,ss for subjects with same bodyweight, same disease severity and twice higher hsCRP value at baseline.
- The observed concentrations were lower in severe HS subjects (Hurley stage III) when compared to moderate and less severe subjects (Hurley stages I and II) (**Figure 4**). The population PK analysis estimated a 15% lower Cavg,ss in Hurley stage III subjects when compared to Hurley stages I and II subjects with the same bodyweight and same hsCRP value at baseline. The exposure decrease was attributed to the increase in clearance of 18% (0.284 L/day in HS subjects with Hurley stage III compared to 0.241 L/day in HS subjects with Hurley stages I and II).
- The terminal half-life (T1/2) for the overall HS population was estimated to be 23 days with an inter-patient variability of 41%.

When combining baseline hsCRP and disease severity effects, the population PK analysis estimated the extent of difference to:

- 25% lower Cavg,ss for Hurley stage III subjects with hsCRP baseline value of 11 mg/L (subgroup median) compared to Hurley stages I and II subjects with hsCRP baseline value of 5 mg/L (subgroup median).
- 50% lower Cavg,ss for Hurley stage III subjects with hsCRP baseline value of 37 mg/ (subgroup 75% quantile) compared to Hurley stage I and II subjects with hsCRP baseline value of 2 mg/L (subgroup 25% quantile).

Figure 2 Distribution of observed trough concentration in HS and PsO adult patients, by visit and treatment

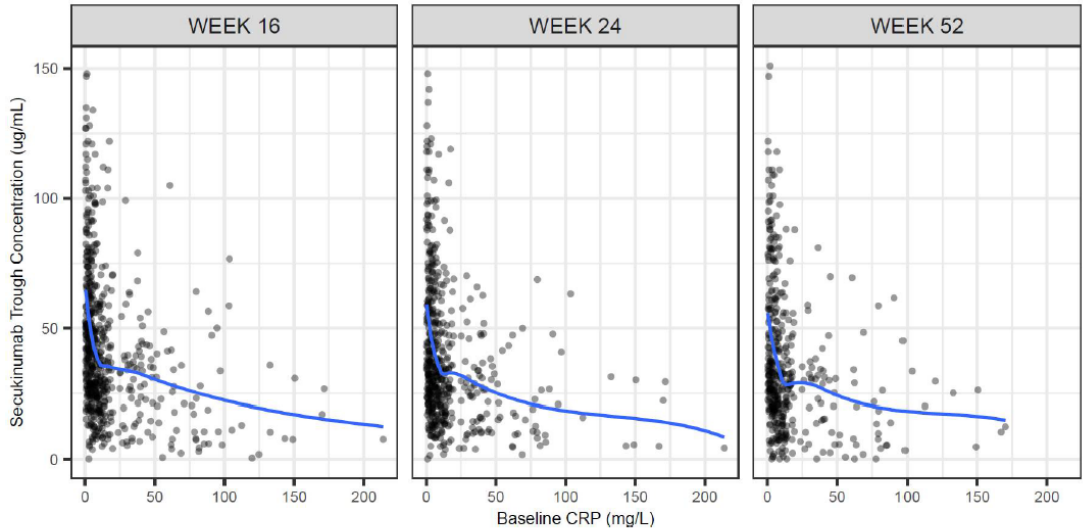


Dots: Observed trough secukinumab concentrations from subjects from Phase 3 PsO studies A2302, A2303, A2308, A2324 and Phase 3 HS studies M2301 and M2302. Placebo-switchers are not included in the figure. Dots are horizontally jittered to ensure legibility.

N represents the number of observed trough concentrations. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range (IQR) beyond the box or the more extreme values whichever is closer to the box.

Source: [AIN457M Modeling report-Figure 5-3]

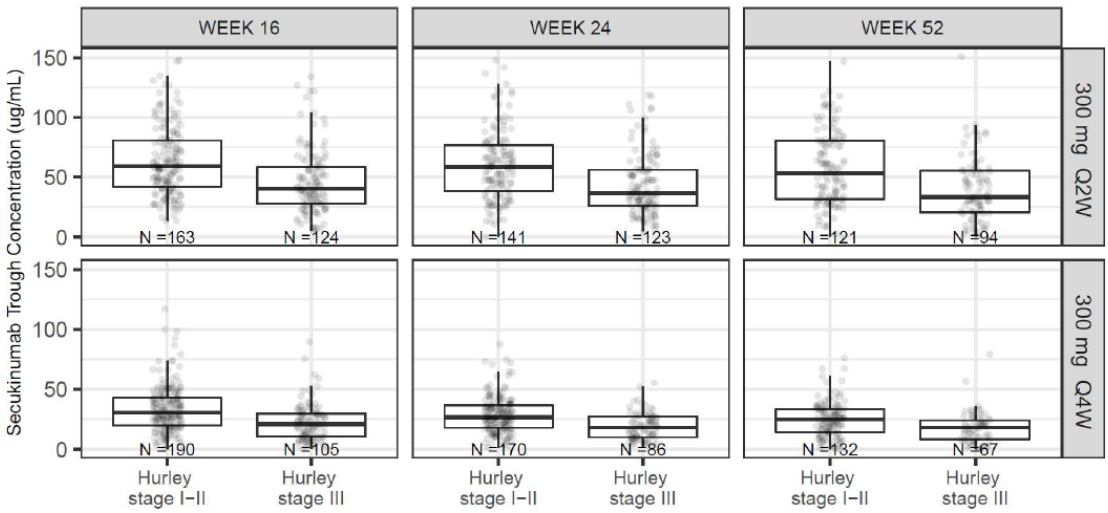
Figure 3 Distribution of observed trough concentration in HS subjects vs. hsCRP baseline value



Dots: Observed trough secukinumab concentrations from subjects in the two Phase 3 HS studies M2301 and M2302. Placebo switchers are not included in the figure. Blue line is smooth loess line.

Source: [AIN457M Modeling report-Figure 5-4]

Figure 4 Distribution of observed trough concentration in HS subjects according to disease severity (Hurley stage)



Dots: Observed trough secukinumab concentrations from subjects in the two Phase 3 HS studies M2301 and M2302. Dots are horizontally jittered to ensure legibility. Placebo switchers are not included in the figure. N represents the number of observed trough concentrations. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range (IQR) beyond the box or the more extreme values whichever is closer to the box.

Source: [AIN457M Modeling report-Figure 5-5]

2.3.3. PK/PD modelling

Exposure-responses analyses were performed on the two pivotal HS Phase 3 studies M2301 and M2302. Exposure-response analyses were cross sectional in nature, and performed at relevant time points (Weeks 16, 24, 40 and 52).

The Exposure-Response (E-R) analysis included PK and efficacy data from the two HS studies (M2301 and M2302). The following efficacy endpoints were considered: Primary endpoint HiSCR50 (HS Clinical

Response), Flare, Skin Pain: Numerical rating scale (NRS30), Abscesses and inflammatory nodule (AN) 50% response (AN50), Absolute and percentage change from baseline in AN count, Hidradenitis Suppurativa-Physician's Global Assessment (HS-PGA) and Dermatology Life Quality Index (DLQI-PRO).

A total of 1042 HS patients contributed to the E-R analysis. Of note, the analyses did not take into account for difference in response rate at Week 4 despite the same loading regimen over the first four weeks between the two regimens. The models are considered to be for descriptive purposes only (as a smoother) and interpretation restricted to the visual appearance of the exposure response curves. Model-estimated parameters such as EC50 are not reported and are not used to draw conclusions.

The analyses were performed on all subjects as well as in subgroups defined based on concomitant use of antibiotics, previous exposure to biologics, baseline disease status (Hurley stages I and II versus stage III), body weight (<90 kg versus >90 kg), study and dose regimen.

The analyses were performed on:

- Binary endpoints: HiSCR50 response, NRS30 response, AN50 response and flares.
- Continuous endpoints: absolute change from baseline in AN count, percentage change from baseline in AN count, HS-PGA and DLQI total score.

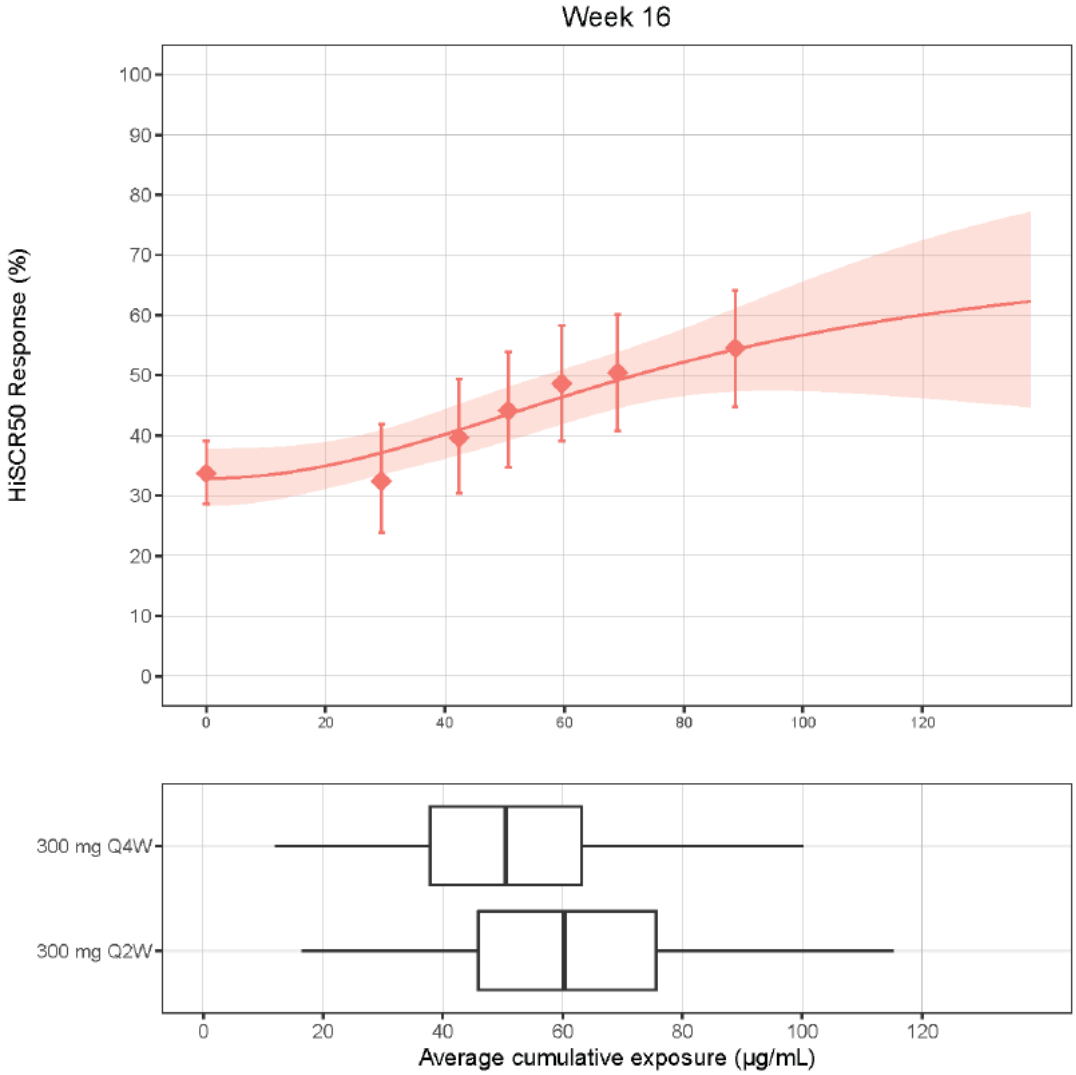
Exposure metrics presented here were predicted using the population PK model at different time points:

- Average cumulative exposure (Cavg,cum) from time 0 to time of efficacy assessment at Week 16
- Average exposure at steady state over a dosing interval (Cavg,ss) for the exposure response assessment at Week 52.

For the primary efficacy endpoint HiSCR50, the exposure-response analysis at Week 16 showed a small benefit of Q2W over Q4W mainly due to the large overlap of exposure. At the individual level, the analysis showed an incremental benefit for subjects achieving high exposure compared to low exposure (**Figure 5**). The benefit of being exposed to secukinumab levels achieved by the Q2W regimen became more prominent over time beyond Week 16 (response rate increase of approximately 5.4% at Week 52 for Q2W compared to Q4W based on median exposure) compared to the Q4W regimen (**Figure 6**). The plateau achieved at high exposure (**Figure 6**) indicates no additional clinical benefit in increasing the dose strength or the frequency of administration beyond 300 mg Q2W.

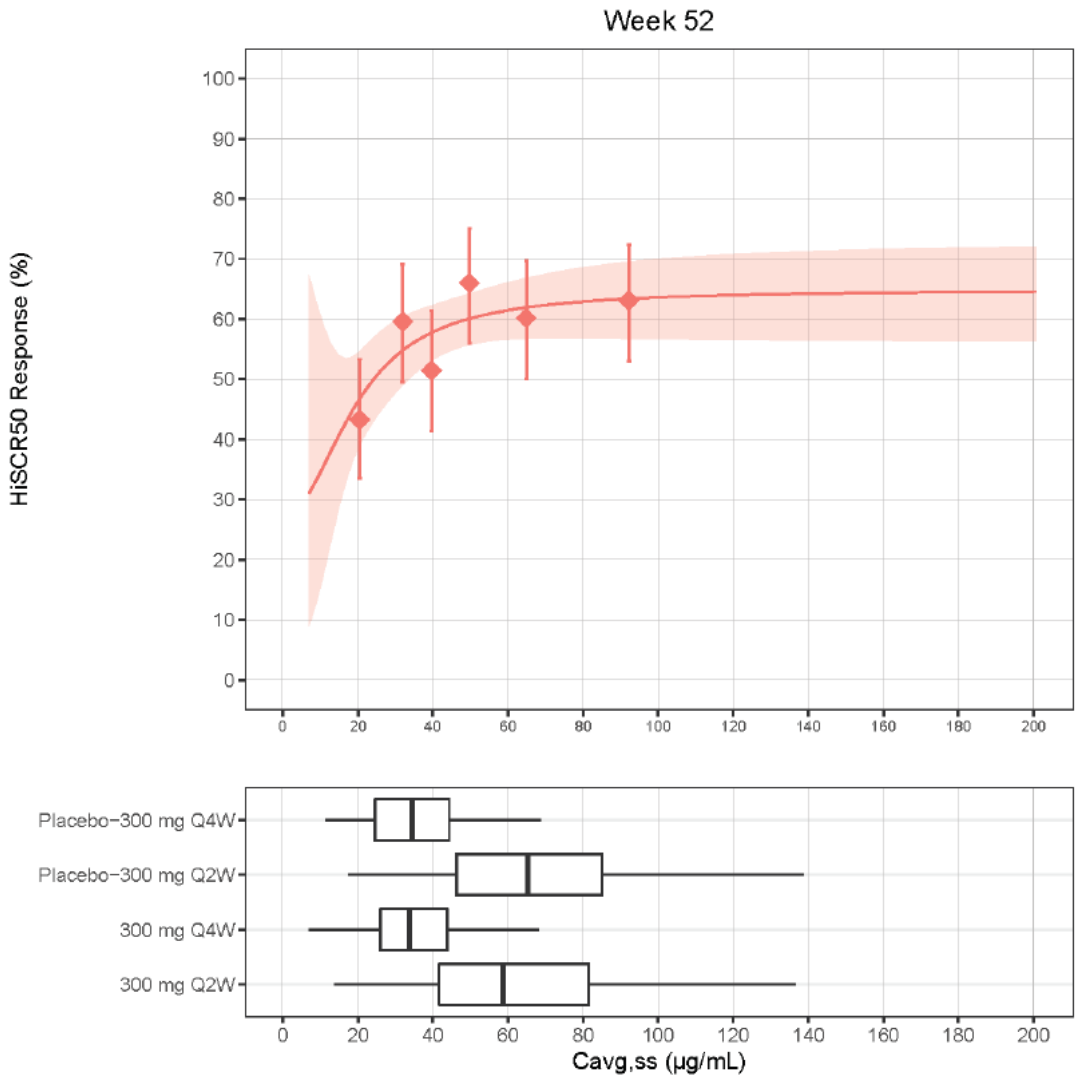
Similar conclusions hold when stratifying by the different subgroups mentioned above. In particular, exposure-response analysis for HiSCR50 demonstrated similar relationships between light subjects (<90 kg) and heavy subjects (≥90 kg) at Week 16 (**Figure 7**) and Week 52 (**Figure 8**) indicating the consistent benefit of Q2W over Q4W for light and heavy subjects. **Figure 9** shows the HiSCR50 response rates as a function of exposure, stratified by baseline disease severity (Hurley stage).

Figure 5 HiSCR50 Response versus Cavg,cum at Week 16 comparing Q2W and Q4W dose regimens



Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)
Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range
Source: [AIN457M Modeling report-Figure 5-11]

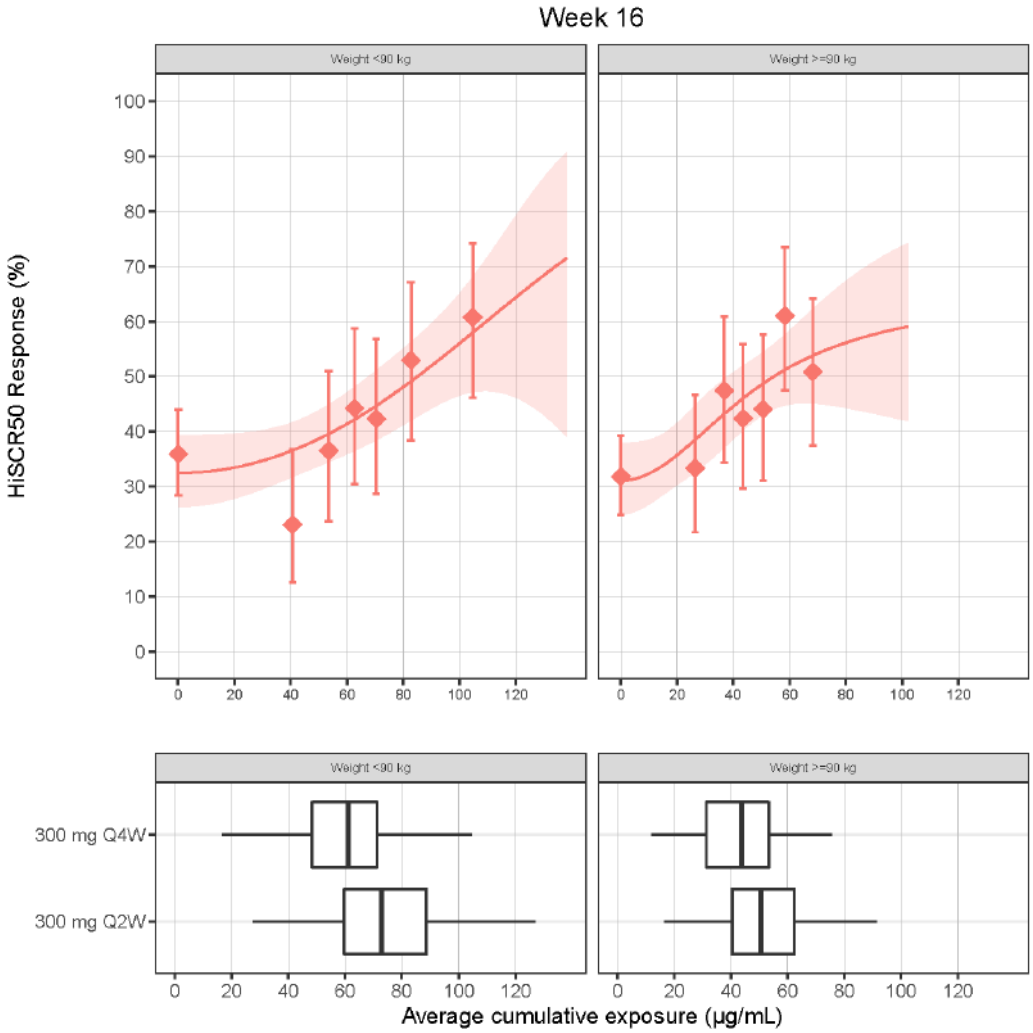
Figure 6 HiSCR50 Response versus Cavg,ss at Week 52 Comparing Q2W, Q4W, Placebo to Q2W and Placebo to Q4W dose regimens



Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)
Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range

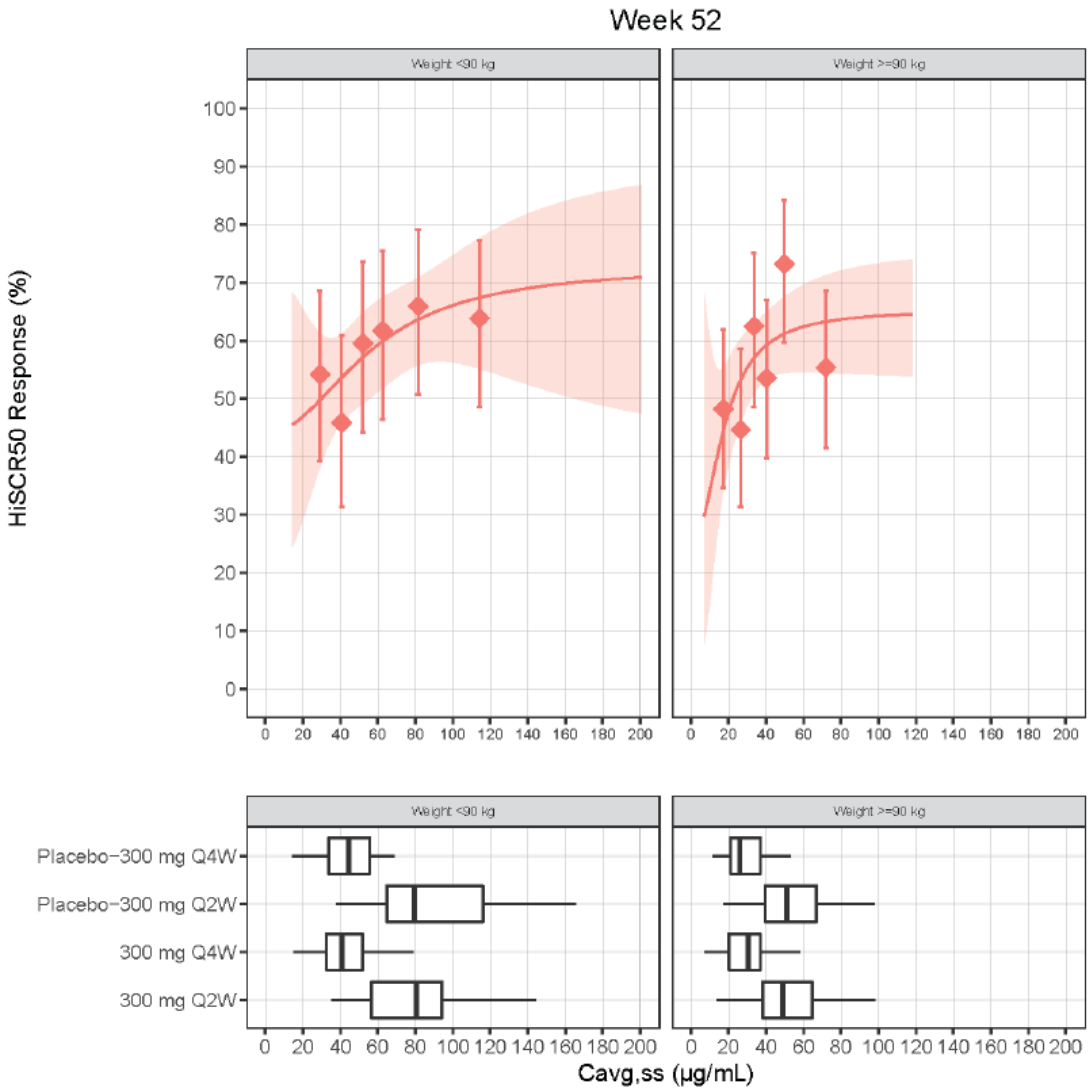
Source: [AIN457M Modeling report-Figure 5-51]

Figure 7 HiSCR50 Response versus Cavg,cum at Week 16 stratified by body weight



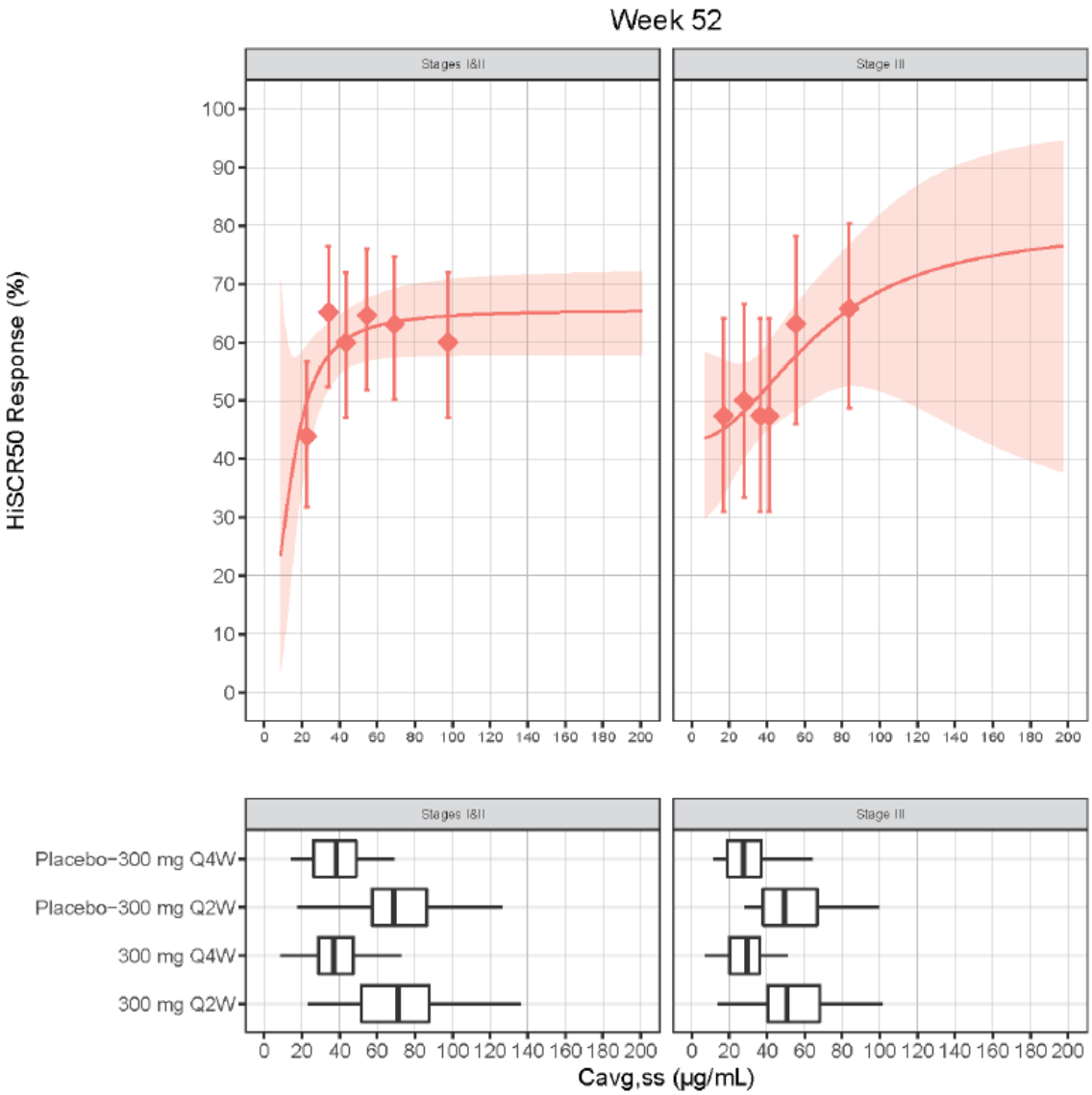
Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)
Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range
Source: [AIN457M Modeling report-Figure 9-22]

Figure 8 HiSCR50 Response versus Cavg,ss at Week 52 stratified by body weight



Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)
Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range
Source: [AIN457M Modeling report-Figure 9-32]

Figure 9 HiSCR50 Response versus Cavg,ss at Week 52 stratified by baseline disease severity (Hurley Stage)

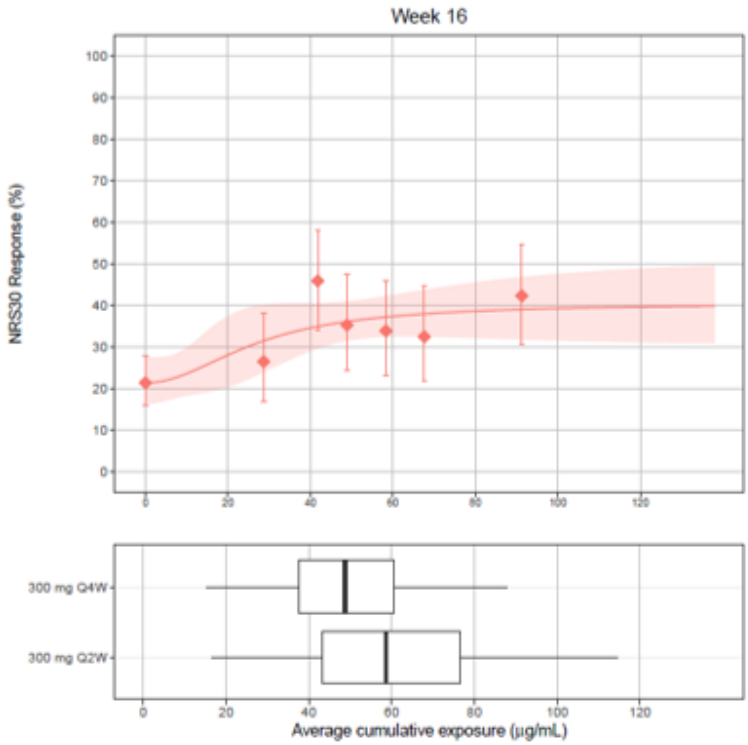


Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar) Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range

For the secondary efficacy endpoint NRS30 (pain), the exposure-response analysis at Week 16 showed a small benefit of Q2W over Q4W mainly due to the large overlap of exposure. At the individual level, it showed an incremental benefit for subjects achieving high exposure compared to low exposure (**Figure 10**). The benefit of being exposed to secukinumab levels achieved by the Q2W dose regimen became more prominent over time beyond Week 16 (approximately 6.0% higher at Week 52 for Q2W based on median exposure) compared to the Q4W dose regimen (**Figure 11**).

Similar conclusions hold when stratifying by the different subgroups mentioned above for the sensitivity analyses indicating that the benefit of Q2W over Q4W was consistent across subgroups. In particular, the exposure-response relationship between light subjects (<90 kg) and heavy subjects (⩾90 kg) at Week 16 (**Figure 12**) and Week 52 (**Figure 13**) showed consistent benefit of Q2W over Q4W for light-weight subjects and heavy-weight subjects.

Figure 10 NRS30 Response versus Cavg,cum at Week 16 Comparing Q2W and Q4W dose regimens

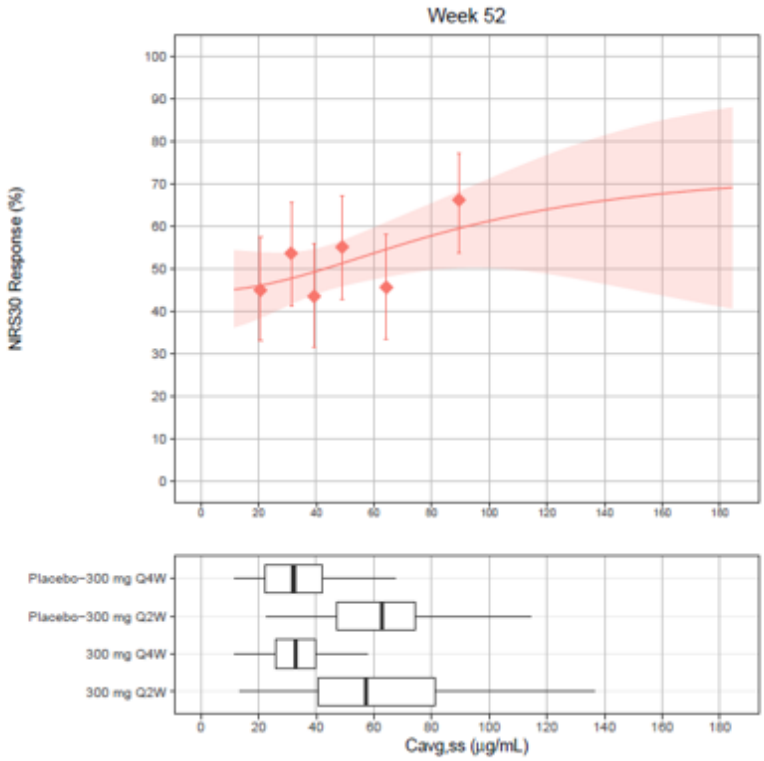


Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)

Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range

Source: [AIN457M Modeling report-Figure 5-12]

Figure 11 NRS30 Response versus Cavg,ss at Week 52 Comparing Q2W, Q4W, Placebo to Q2W and Placebo to Q4W dose regimens

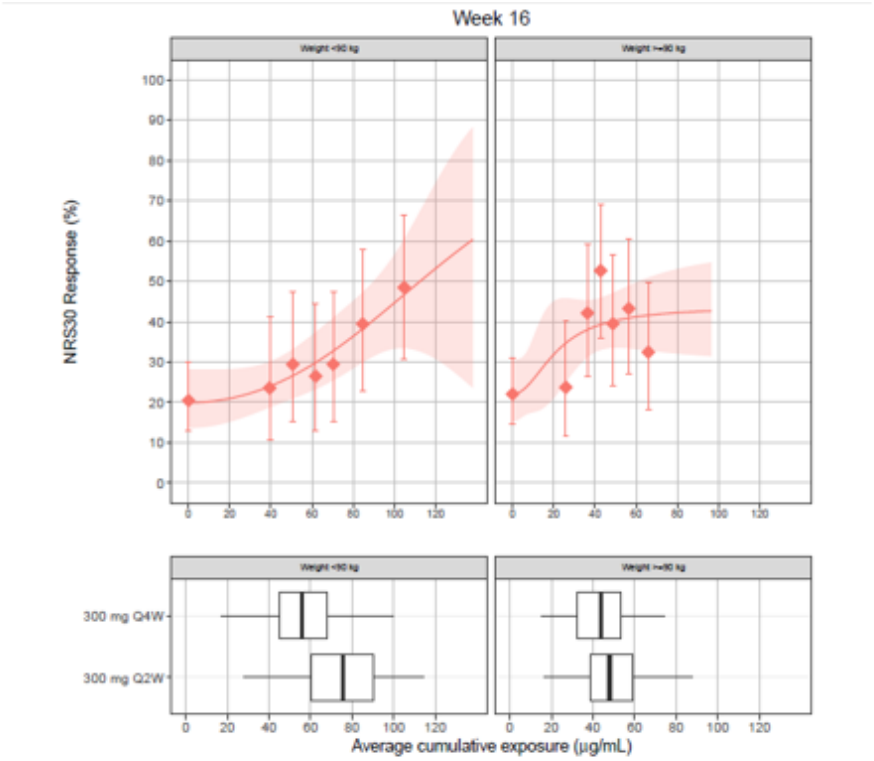


Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)

Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range

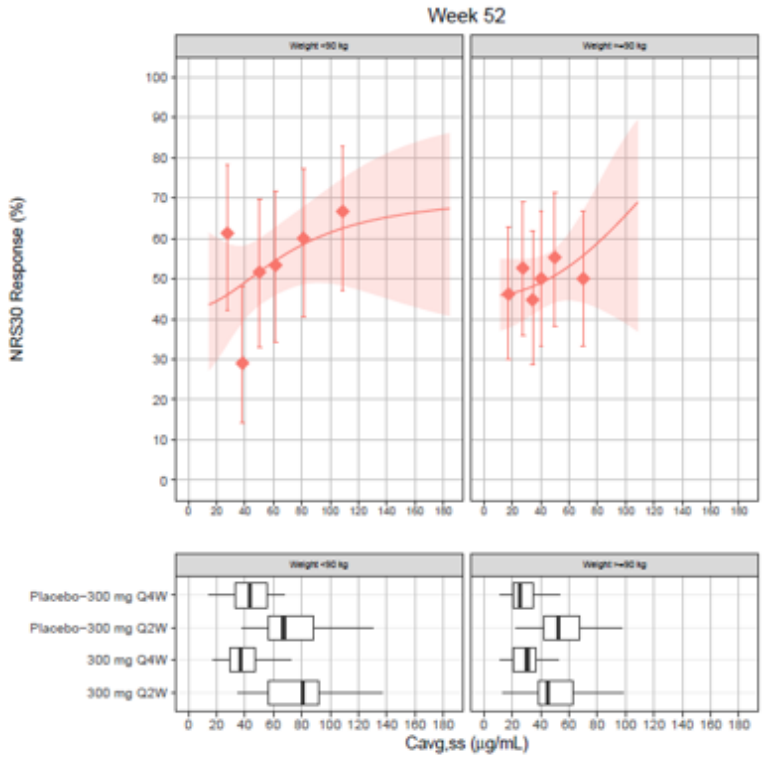
Source: [AIN457M Modeling report-Figure 5-52]

Figure 12 NRS30 Response versus Cavg,cum at Week 16 stratified by body weight



Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)
Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range
Source: [AIN457M Modeling report-Figure 9-22]

Figure 13 NRS30 Response versus Cavg,ss at Week 52 stratified by body weight



Top: Red line: Predicted response rate with 95% confidence interval (shaded area). Diamonds are observed response rate with 95% confidence limits (error bar)
Bottom: Predicted exposure from pivotal HS Phase 3 studies M2301 and M2302. The lower and upper ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers extend to the 1.5 time the interquartile range
Source: [AIN457M Modeling report-Figure 9-32]

2.3.4. Discussion on clinical pharmacology

The MAH has collected sparse trough PK samples from all patients at baseline and weeks 16, 24, 52 and 60. The trough secukinumab concentrations observed in HS patients are lower than the trough concentrations observed in earlier clinical studies in psoriatic patients. Moreover, the MAH has conducted population PK modelling on the basis of 11 PsO studies and the two pivotal HS phase 3 studies. The population PK modelling suggested that the clearance of secukinumab is higher in HS patients, and that patients with severe baseline disease have yet higher clearance than patients with less severe baseline disease.

The bioanalytical method was identical to methods used in other indications except for LLOQ, which was updated from 80 ng/ml to 160 ng/ml due to observed plate effect at 80 ng/ml. The plate effect was not observed at 160 ng/ml and the measured samples with results between 80 ng/ml and 160 ng/ml were remeasured. The change in the LLOQ had no effect on the PK results.

Secukinumab concentrations after 300 mg Q2W dosing regimen were twice as high as after 300 mg QW4 in HS patients, indicating linear PK.

The population PK model was based on previous modelling performed with data from PsO patients. This is considered appropriate. The model diagnostics (goodness of fit plots; prediction-corrected visual predictive check; plots of clearance random effects versus covariates) did not show signs of model misspecification.

The population PK model only considered the possibility that HS patients might have lower trough concentrations because of increased clearance and did not consider the possibility that the lower trough concentrations might be a result of lower bioavailability. However, given the sparsity of PK data in HS patients, it is unlikely that population PK modelling could statistically identify whether the low trough concentrations in HS patients result from alterations in clearance or bioavailability. Moreover, alterations in clearance seem more likely since inflammatory status has been identified in the scientific literature to correlate with monoclonal antibody clearance (ref: https://doi.org/10.1002%2Fpsp4.12224). Finally, even if the low trough concentrations in HS patients were caused by a bioavailability difference and not a clearance difference, it would not change the overall conclusions on suitability of the proposed dosing regimen. Therefore, the issue of potential secukinumab bioavailability differences in HS patients was not pursued by the CHMP.

Population PK modelling suggested that antibiotics have no interactions with secukinumab, however the conclusions are limited by the sparsity of PK sampling. Antibiotics contain a large group of different drugs, and antibiotic use was only tested as a dichotomous yes/no variable; this ignores differences between antibiotics, and also ignores the duration and dose level of antibiotics. As such, the conclusions reached by the current analysis are limited. No SmPC changes with regard to antibiotics DDI potential are proposed by the MAH, and this is supported by the CHMP.

The exposure-response analyses were cross-sectional in nature, which means that the analyses were conducted independently at several timepoints, without considering that the responses might be correlated over time. This is a limitation. It would be relevant to consider the correlation between responses over time because the response rates at week 4 were higher for the Q4W group than for the Q2W group. This suggests that for one reason or another, the Q4W group subjects may have been more sensitive to respond to secukinumab. If this is the case, then between-group imbalances may obfuscate the exposure-response relationships, because the currently conducted analyses do not consider correlations between responses over time. The MAH attempted to fit longitudinal PK/PD model of subject specific HiSCR50 response profiles over time (which would take into account that the responses may correlate over time), however such a model could not be robustly estimated. While it is acknowledged that fitting a longitudinal PK/PD model to a single dichotomous response variable may not be feasible, it seems possible that a longitudinal PK/PD latent variable model of all primary and secondary endpoints could have been successful in describing the data. There are examples of longitudinal item response theory models which could have been adapted to the current dataset (see e.g., https://doi.org/10.1002/psp4.12601). However, such a model is not strictly necessary in order to evaluate the benefit-risk of secukinumab in HS patients, therefore, this issue was not pursued, and the MAH was not requested for additional exposure-response modelling efforts.

Given that there is between-subject variability in secukinumab PK and given that previous PK-PD analyses in psoriatic patients have indicated high between-subject variability in the concentrations required to elicit a therapeutic response, the MAH was requested to further justify the benefit of starting with Q2W dosing, instead of starting with Q4W dosing with the option to titrate to Q2W dosing on the basis of treatment response. In response, the MAH has modified the posology in patients with moderate and severe hidradenitis suppurativa (HS) and proposed a dose-escalation strategy. The recommended dose in HS patients is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks.

The proposed SmPC section 5.2 changes (addition of information on absorption and elimination) are acceptable.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology package supports the extension of indication to HS patients and the proposed dosing frequency Q4W after the initial four weekly injections and the possibility to increase the dosing Q2W based on clinical response is acceptable from the pharmacokinetic point of view.

2.4. Clinical efficacy

2.4.1. Dose response studies

No separate dose response studies were conducted. The MAH justified dose selection for the main studies on the following grounds:

Rationale for 300 mg s.c. every 4 weeks regimen

Secukinumab 300 mg Q4W is approved for the treatment of adult patients with moderate to severe plaque PsO, an inflammatory dermatological disease affecting the superficial layers of the skin and with moderate inflammatory burden. Considering the involvement of the Th17-related pathways in HS, and the positive clinical efficacy demonstrated by this secukinumab dose regimen in case reports in subjects with HS, the inhibition of IL-17A via secukinumab 300 mg Q4W was expected to provide a positive benefit-risk in moderate to severe HS patients, justifying further evaluation.

This dose regimen is in line with the authorised posology in moderate to severe plaque psoriasis, and initial information from case reports showed a positive clinical response with this regimen in HS.

Rationale for 300 mg s.c. every 2 weeks regimen

Secukinumab 300 mg Q2W was evaluated to achieve a higher exposure for the following reasons:

- Secukinumab systemic exposure varies with body weight in an allometric relationship. For clearance, the allometric exponent was estimated to be close to 1; in other words, a doubling of body weight could lead to a nearly 2-fold increase in clearance and, therefore, reduced serum exposure. Since higher body weights were expected in HS than in PsO (approximately 10 kg heavier weight in clinical trials), HS may require a dose regimen with higher exposure than that resulting from the marketed regimen.
- Higher exposure than in PsO might be needed due to nature of HS lesions which are deeper in the dermis and more inflamed.
- Feedback from the medical community and the experts included in the HS program Steering Committee advised the evaluation of a higher dose regimen due to the severe and progressive nature of the disease and the well-described diagnostic delay leading to patients presenting to medical care in advanced states. Moreover, the clinical experience with adalimumab in HS confirmed the need of a dose regimen with higher exposure to treat this patient population.

At the time of the study initiation, the secukinumab 300 mg Q2W dose regimen had been tested in over 300 subjects for at least 24 weeks in completed clinical studies in uveitis and PsO. Moreover, after the initiation of studies M2301 and M2302, a randomised, double-blind, multicentre study [Study A2324] was conducted in adult subjects with moderate to severe plaque PsO weighing ≥90 kg to evaluate efficacy and safety of the secukinumab 300 mg Q2W dose regimen in comparison with the secukinumab 300 mg Q4W dose regimen. The study demonstrated clinical benefit of the secukinumab 300 mg Q2W dose regimen over the Q4W dose regimen in this PsO patient population without increased safety risks, leading to its recent approval in the EU (procedure EMEA/H/C/003729/II/0076), where the authorised posology

now includes the following provision for dose escalation from the standard Q4W maintenance regimen: "Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher."

2.4.2. Main studies

CAIN457M2301 ("SUNSHINE") and CAIN457M2302 ("SUNRISE") A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa

As part of the initial submission, the MAH submitted Week 16 interim clinical study reports for both studies, with Week 52 data being included for some 65% of subjects. Additional data based on the full 52 week datasets were provided as part of the MAH response to the RSI.

As the studies were identical in design and the MAH has conducted analyses pooling results from the two studies, the Methods and Results sections present the studies together, with differences between the studies highlighted as relevant.

Methods

Studies M2301 and 2302 were multicentre, randomised, double-blind, placebo-controlled, parallel group studies with two secukinumab dose regimens in subjects with moderate to severe HS. Each study consisted of: Screening (up to 4 weeks), placebo-controlled Treatment Period 1 (16 weeks) and Treatment Period 2 (36 weeks, all subjects on secukinumab). Both dose regimens started with an induction period (300 mg loading injections at Baseline, Weeks 1, 2, 3, and 4), followed by the maintenance treatment at the specified dosing frequency (Q2W or Q4W). Subjects who completed Treatment Period 1 then entered Treatment Period 2. Subjects who were randomised to either of the two secukinumab dose regimens continued on the same dose regimen. Subjects who were randomised to either of the two 'Placebo to secukinumab' regimens received secukinumab 300 mg at Weeks 16, 17, 18, 19, and 20 as loading injections, then at the randomised schedule of either Q2W or Q4W thereafter. Both studies were conducted in double-blind fashion for their entire duration (52 weeks). Subjects who prematurely discontinued the study, or who completed the study and could not or did not wish to continue in the optional extension study, were required to complete a post-treatment follow-up period (8 weeks). Key elements of the studies are outlined in **Table 3**, and the study design is graphically depicted in **Figure 14**.

Table 3 Key elements of studies M2301 and M2302

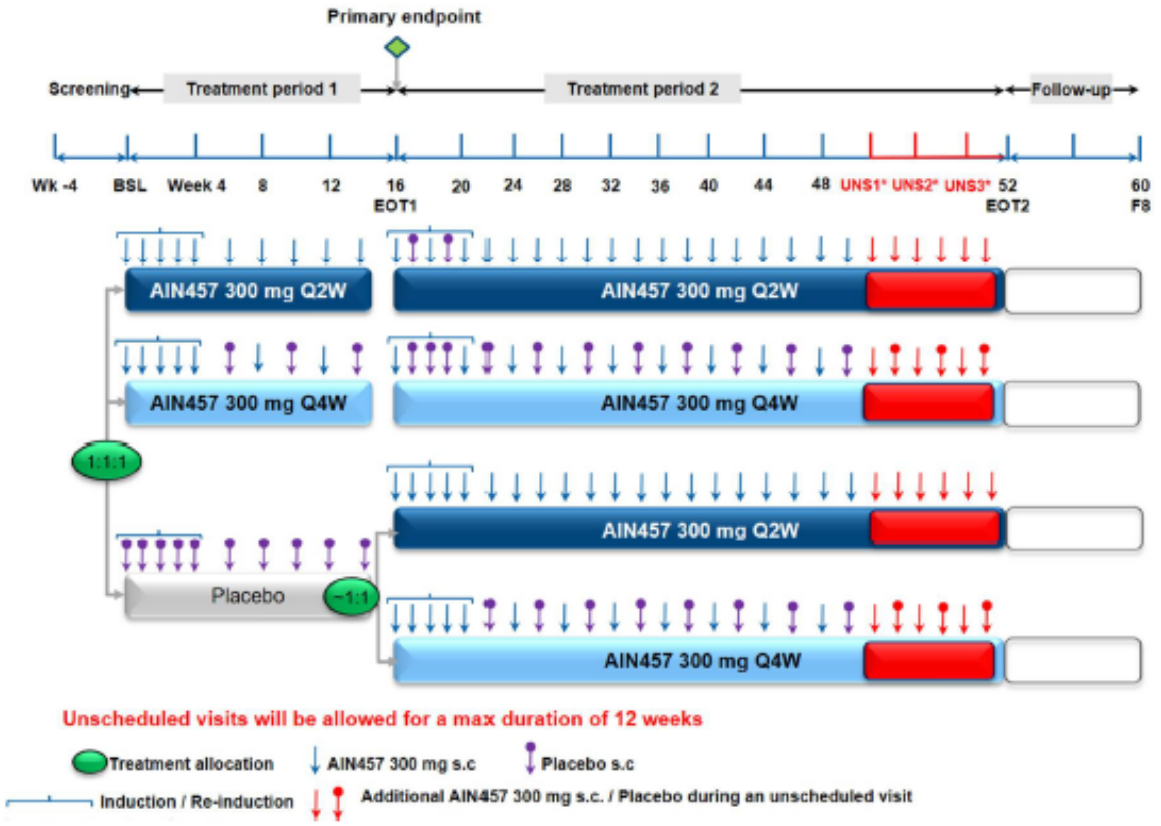
Key features			
Controlled study	Yes		
Phase	3		
Study design	Multi-center, randomized, double-blind, placebo-controlled, parallel group		
Population	Adults aged 18 and older with moderate to severe HS		
Treatment duration	A total of 52 weeks: • Treatment Period 1: 16 weeks (either AIN457 or placebo) • Treatment Period 2: 36 weeks (all subjects on AIN457)		
No. participants per Treatment(s)		M2301	M2302
	• Total number of subjects randomized and included in RAS* and FAS*:	541	543
	◦ AIN457 300 mg Q2W:	181	180
	◦ AIN457 300 mg Q4W:	180	180
	◦ Placebo to AIN457 300 mg Q2W or Placebo to AIN457 300 mg Q4W:	180	183
Key efficacy endpoints	• Primary endpoint: Achievement of HiSCR50 at Week 16 • Secondary endpoints: ◦ Percentage change from baseline in AN count at Week 16 ◦ Flares up to Week 16 ◦ Achievement of NRS30 in HS-related skin pain at Week 16, among subjects with baseline NRS ≥3 A complete list of exploratory endpoints can be found in [Study M2301-Section 8] and [Study M2302-Section 8].		
Completed/Ongoing	Ongoing Primary endpoint analysis data cut-off date: • M2301: 01-Oct-2021 • M2302: 23-Sep-2021		

* Excludes subjects who were mis-randomized or with serious GCP violations at their site (Section 3.1.1).

Source: [Tabular Listing of All Clinical Studies]

Source: SCE Table 1-1

Figure 14 Study design for studies M2301 and M2302 (including changes due to COVID-19)



BSL: Baseline; EOT1/EOT2: End of Treatment 1/2; F8: End of Follow-up visit at Week 60; Q2W: every two weeks; Q4W: every four weeks. *UNS = Unscheduled; UNS1, UNS2 and UNS3 correspond to three possible additional IRT calls at which 2 doses are dispensed if COVID related occurrences required it. These unscheduled IRT calls were introduced in the Protocol Amendment 01 of studies M2301 and M2302.

Treatment allocation for Placebo arm switching to secukinumab arms at Week 16 was performed at the Randomization visit in 1:1 ratio and did not account for potential discontinuations during Treatment Period 1.

Follow-up: only subjects who prematurely discontinued treatment during Treatment Period 1 or 2 or subjects who did not enroll in the extension study, entered Follow-up.

In the event of a global health disruptive event, such as a pandemic/epidemic (e.g., COVID-19), that limits or prevents the conduct of site study visits per protocol, special efforts were made to conduct on-site visits for the EOT(s) visits, Week 16 and Week 52.

Source: [Study M2301-Figure 9-1], [Study M2302-Figure 9-1]

Source: SCE Figure 1-1

The effects of treatment discontinuation are being studied in a currently ongoing HS extension study M2301E1. Study M2301E1 is a four-year long-term extension study, and its purpose is to evaluate the effect of treatment interruption (randomised withdrawal) and re-treatment with secukinumab on efficacy, tolerability and safety in subjects with moderate to severe HS who completed either of the two Phase III studies, M2301 or M2302. Analyses will include evaluation of time to loss of response, number of flares and the effect of restarting secukinumab therapy on regaining HiSCR. Furthermore, the study will address the question of whether an increase in dose following loss of response is effective in regaining and sustaining clinical response and a favourable risk-benefit ratio as well as the time required to regain HiSCR response after re-treatment following loss of response. The primary endpoint analysis of the extension study will be conducted on data collected at Week 104 (currently estimated for H2 2023).

Study participants

The following main eligibility criteria were applied in both studies:

Main inclusion criteria:

1. Written informed consent was obtained before any assessment was performed.
2. Male and female subjects ≥ 18 years of age.
3. Diagnosis of HS ≥ 1 year prior to baseline.
4. Subjects with moderate to severe HS defined as:
   - A total of at least 5 inflammatory lesions, i.e., abscesses and/or inflammatory nodules,

     and
   - Inflammatory lesions should affect at least 2 distinct anatomic areas
5. Subjects agreed to daily use of topical over-the-counter antiseptics on the areas affected by HS lesions while on study treatment.

Main exclusion criteria:

1. Total fistula count ≥ 20 at baseline, or other active skin disease or condition that may interfere with assessment of HS.
2. Active ongoing inflammatory diseases other than HS that require treatment with prohibited medications or use of, or planned use of, prohibited treatment.
3. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A/F or the IL-17 receptor.
4. History of chronic or recurrent systemic infections or active systemic infections during the last two weeks (exception: common cold) prior to randomization.
5. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years.
6. Pregnant or lactating women or women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using methods of contraception during the entire study or longer if required by locally approved prescribing information.

No additional exclusions could be applied by the Investigator, in order to ensure that the study population was representative of all eligible subjects.

Treatments

The following study treatments were used:

Investigational drug:

- Secukinumab 300 mg solution for s.c. injection in a 2 mL pre-filled syringe

Reference therapy:

- Placebo solution for s.c. injection in a 2 mL pre-filled syringe

Secukinumab PFS and placebo PFS were provided in a double-blind fashion and had identical appearance.

Treatment arms:

At Baseline/Randomisation visit, all eligible subjects were randomised via Interactive Response Technology (IRT) in a 1:1:0.5:0.5 ratio to one of the following 4 treatment groups:

- Secukinumab 300 mg every 2 weeks (Q2W) group: subjects were to receive a loading dose of secukinumab 300 mg once weekly for four weeks (at Randomisation, Weeks 1, 2, 3 and 4), followed by secukinumab 300 mg every two weeks, starting at Week 6 and up to Week 50. These subjects were to receive two additional placebo injections at Weeks 17 and 19 to maintain the treatment blind during the re-induction.
- Secukinumab 300 mg every 4 weeks (Q4W) group: subjects were to receive secukinumab 300 mg once weekly for four weeks (at Randomisation, Weeks 1, 2, 3 and 4), followed by secukinumab 300 mg every four weeks, starting at Week 8 and up to Week 48. In order to maintain the treatment blind, subjects in this group were to also receive a placebo injection every 4 weeks starting at Week 6, until Week 50. These subjects were to receive three additional placebo injections at Weeks 17, 18 and 19 to maintain the treatment blind during the re-induction.
- Placebo group to secukinumab 300 mg Q2W: subjects were to receive placebo once weekly for four weeks (at Randomisation, Weeks 1, 2, 3 and 4), followed by placebo every two weeks, starting at Week 6 and up to Week 14. At Week 16, subjects were to be switched from Placebo to Secukinumab 300 mg every 2 weeks. The subjects were to receive secukinumab 300 mg once weekly for four weeks (Weeks 16, 17, 18, 19 and 20), followed by secukinumab 300 mg every two weeks, starting at Week 22 and until Week 50.
- Placebo group to secukinumab 300 mg Q4W: subjects were to receive placebo once weekly for four weeks (at Randomization, Weeks 1, 2, 3 and 4), followed by placebo every two weeks, starting at Week 6 and up to Week 14. At Week 16, subjects were to be switched from Placebo to Secukinumab 300 mg every 4 weeks. The subjects were to receive secukinumab 300 mg once weekly for four weeks (Weeks 16, 17, 18, 19 and 20), followed by secukinumab 300 mg every four weeks, starting at Week 24 and up to Week 48. To maintain the treatment blind, subjects were to receive placebo alternating with secukinumab starting at Week 22 and up to Week 50.

Concomitant treatments:

Subjects were requested to use daily topical over-the-counter antiseptics or wound care dressings on the skin areas affected by HS lesions following local standard practice.

Systemic antibiotics for the treatment of acute systemic infectious disease both related or unrelated to HS (e.g., pneumonia, cellulitis) were allowed as medically warranted during the study. Prior to Week 16, systemic antibiotics for the treatment of HS (minocycline or doxycycline up to 100 mg b.i.d.) were only allowed as rescue medication. For subjects entering the study in the antibiotic strata, treatment with tetracycline up to 500 mg b.i.d., minocycline up to 100 mg b.i.d., and doxycycline up to 100 mg b.i.d. on stable dose was allowed.

At Week 4, 8 and 12, if a subject experienced an increase in their AN count (for example, the total count was $\geq$ 150% of the weighted average of screening and baseline AN count with a minimum increase of 3 lesions), oral antibiotics could be used as rescue medication. This applied only to Treatment Period 1.

Subjects were required to wash-out any ongoing opioid analgesics (including tramadol) for 14 days prior to Baseline. In case a subject presented with uncontrolled pain related to HS during the study, ibuprofen and acetaminophen (paracetamol) was used. If the HS pain was still not controlled with ibuprofen or paracetamol at the maximal dose as per local label, tramadol (at a dose of up to 100 mg orally every

4 hours) could be prescribed. The use of other opioid analgesics was prohibited during participation in the study.

The study protocols included a table of other prohibited medications, such as immunomodulatory drugs, systemic corticosteroids, and live vaccines, outlining required wash-out periods prior to randomisation.

Objectives and endpoints

The purpose of the development plan with twin studies M2301 and M2302 was to demonstrate the efficacy and safety of two dose regimens of secukinumab at Week 16 based on HiSCR50 rates versus placebo, along with the maintenance of efficacy and safety of secukinumab up to Week 52, in subjects with moderate to severe HS. The stated objectives of studies along with their associated endpoints are listed in **Table 4**.

Table 4 Objectives and endpoints for studies M2301 and M2302

Objectives	Endpoints
Primary objectives	
• To demonstrate the efficacy of secukinumab compared to placebo with respect to HiSCR after 16 weeks of treatment.	• Achievement of HiSCR at Week 16. HiSCR is defined as at least a 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae.
Secondary objectives	
• To demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to AN count.	• Percentage change from baseline in AN count at Week 16.

• To demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to:
  • proportion of patients with HS flares
  • proportion of patients with clinical response in HS related skin pain
	• Flaring up to Week 16. Flare is defined as at least a 25% increase in AN count with a minimum increase of 2 AN relative to baseline.
	• Achievement of NRS30 (skin pain) at Week 16, among subjects with baseline NRS ≥ 3. NRS30 is defined as at least a 30% reduction and at least 2 unit reduction from baseline in Patient's Global Assessment of Skin Pain - at worst.

Exploratory objectives	
• To evaluate the safety and tolerability of secukinumab over 52 weeks of treatment.	• Clinical safety and tolerability assessments including physical exams, vital signs, laboratory assessments, AE monitoring
• To explore the long-term effect of secukinumab with respect to HiSCR, AN count, proportion of patients with flares, HS related skin pain up to 52 weeks of treatment.	• Achievement of clinical response as defined by HiSCR, absolute and percentage change from baseline in AN count, flares, achievement of pain relief as defined by NRS30 (skin pain).

• To evaluate the effect of secukinumab with respect to the following efficacy assessments:
  • Modified Hidradenitis Suppurativa Score (mHSS);
  • HS-Physician's Global Assessment (HS-PGA);
  • Dermatology Life Quality Index (DLQI);
  • Health Status Questionnaire (EQ-5D-3L);
  • Patient Global Impression of severity (PGI-s);
  • Patient Global Impression of change (PGI-c);
  • Work Productivity and Activity Impairment (WPAI);
  • HS Symptom Diary
  • Inflammatory markers with respect to CRP and ESR compared to placebo after 16 weeks, and in the two secukinumab dose regimens up to 52 weeks of treatment.
	• Absolute and percent change from baseline in modified Hidradenitis Suppurativa Score (mHSS).
	• HS-PGA response. HS-PGA response is defined as the achievement of at least a 2-point reduction in HS-PGA score compared to baseline or the achievement of a "mild" status (defined as achieving an HS-PGA score of ≤ 2).
	• DLQI response and absolute/percent DLQI total score change from baseline.
	• DLQI response is defined as a decrease greater than 5.0 points from baseline.
	• EQ-5D-3L categories on category questions and summary statistics on EQ -5D -3L score questions.
	• Patient global impression of severity and change (PGI-s and PGI-c) categories.
	• Absolute and percent change from baseline in work productivity and Activity Impairment - specific health problem (WPAI-SHP).
	• HS symptom diary items score change from baseline.
	• Absolute and percent change from baseline in CRP and ESR.

• To evaluate the pharmacokinetics of secukinumab in HS patients.	• AIN457 levels in serum
• To assess the development of immunogenicity against secukinumab.	• Anti-AIN457 antibodies levels in serum
• To explore the potential association of biomarker levels with secukinumab efficacy and safety by visit up to Week 52 visit (EOT2).	• Biomarkers in serum
• To explore the efficacy of secukinumab compared to placebo with respect to HiSCR response after 16 weeks of treatment and the sustained efficacy over time in bio-naive patients.	• Achievement of HiSCR at Week 16 and up to Week 52 in bio-naive patients.
• To explore the efficacy of secukinumab compared to placebo with respect to HiSCR response after 16 weeks of treatment and the sustained efficacy over time in patients with body weight lower and higher than 90 kg (<90 kg and ≥90 kg).	• Achievement of HiSCR at Week 16 and up to Week 52 in patients with body weight lower and higher than 90 kg (<90 kg and ≥90 kg).

Source: M2302 CSR Section 8

The following endpoint definitions were applied:

Hidradenitis Suppurativa Clinical Response (HiSCR)

The HiSCR is defined by the status of three types of lesions: abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), and draining fistulae (sinus tracts, with communications to skin surface, draining purulent discharge). The definition of responders to treatment (HiSCR achievers) was:

- at least a 50% reduction in abscesses and inflammatory nodules (ANs),
- no increase in the number of abscesses, and
- no increase in the number of draining fistulas from baseline.

HiSCR75, HiSCR90, and HiSCR100 were defined by increasing the threshold on percentage reduction in AN count to 75%, 90% and 100%, respectively.

The HiSCR was derived from the individual lesion counts of abscesses, nodules and fistulae at scheduled visits. Individual lesion counts were performed for all lesions, including any existing and newly observed lesions. The HS lesions were defined as:

- Inflammatory nodules (N) that are typically raised, deep-seated, three-dimensional, round, tender, erythematous, infiltrated and possibly pyogenic granuloma lesions with a diameter of >10 mm
- Abscesses (A) that are often inflammatory, painful, tender but fluctuating mass with a diameter of >10 mm, surrounded by an erythematous area; the middle of an abscess contains pus
- Draining fistulae (DF); sinus tracts, raised, tender but fluctuating longitudinal mass of variable length and depth, with communications to skin surface, draining purulent fluid
- Fistulae (F): total fistulae defined as sinus tracts, raised, tender but fluctuating longitudinal mass of variable length and depth, with communications to skin surface, both draining and non-draining purulent fluid.

Lesion counts were completed at two Screening visits, Baseline Day 1, Weeks 2, 4, 8, 12 and 16, 18, 20 and every four weeks until week 60.

AN count

AN count is the sum of individual lesions of abscesses and inflammatory nodules in the HS affected areas as assessed by the physician.

Flare

A flare was defined as at least a 25% increase in AN count with a minimum increase of 2 in absolute AN count relative to baseline.

Skin Pain - NRS

The Patient's global assessment of skin pain - NRS in the past 24 hours was used to assess pain "at its worst" and the average skin pain due to HS in the last 24 hours. The NRS is a segmented numeric version of the visual analogue scale in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of their pain ranging from 0 (no skin pain) to 10 (skin pain as bad as you can imagine).

NRS30 (skin pain) was defined as at least a 30% reduction and at least 2 units reduction from baseline in Patient's Global Assessment of Skin Pain - at worst. The Patient's Global Assessment of Skin Pain - NRS

was completed by the subject using an eDiary device. NRS30 response was primarily evaluated in subjects with baseline NRS ≥3; in response to a presubmission request, the MAH also provided analyses for the FAS without regard to baseline NRS.

Sample size

Sample size of the studies was primarily driven by HiSCR at Week 16 endpoint. A total of 471 subjects was originally planned to be randomised to study drug in a 1:1:0.5:0.5 ratio.

Both studies were independently powered to address the primary endpoint (HiSCR) and secondary endpoints of AN count and flare. In terms of HiSCR, based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively, Kimball et al 2016), a placebo response rate of 30% is assumed. The total sample size of 471 subjects for this trial was considered sufficient to achieve 93% power for the demonstration of 20% difference of secukinumab 300 mg Q2W over placebo when assuming the secukinumab response rate to be 50%. In regard to the comparison of secukinumab 300 mg Q4W to placebo, the power was to show superiority was expected to be 83%.

The secondary endpoint of pain was analysed in the combined populations of both trials, provided the primary null-hypothesis could be rejected in both studies.

Due to COVID-19 pandemic, the number of randomised subjects was increased to approximately 541 (15% increase from the original population of 471 subjects) by protocol Amendment 01.

Randomisation

Each subject was identified in the study by a subject number that was assigned when the subject was enrolled for screening. After confirming the subject inclusion/exclusion criteria, IRT was contacted to assign a randomisation number to the subject, which was used to link the subject to a treatment arm. The randomisation number was not communicated to the Investigator or his/her delegate. Randomisation was stratified by region, concomitant antibiotic use and body weight.

Blinding (masking)

This is a double-blind study. Subjects, site staff, persons performing the assessments, and Novartis clinical trial team remained blinded to the identity of the treatment from the time of randomisation until database lock with exception of drug supply management, vendors whose roles required unblinding. At the time of the interim database lock, the study team members involved in primary endpoint analysis separated from the blinded study team had access to the unblinded results as described in the unblinding charter. These members were no longer directly involved in the conduct of the trial after primary analysis interim database lock.

Statistical methods

The following analysis sets were used for the data analysis.

- Randomised analysis set: consisted of all randomised subjects. Subjects were analysed according to the treatment they were assigned to at randomisation. Unless otherwise specified, mis-randomised subjects (mis-randomised in IRT) were excluded from the randomised analysis set. Mis-randomised subjects are subjects who were screen-failures but had been randomised by the Investigator before eligibility was finally assessed, however had not been treated.

Furthermore, all subjects with serious GCP violation at their site were excluded from the randomised analysis set.

- Full analysis set: consisted of all subjects to whom study treatment had been assigned. Subjects were analysed according to the treatment assigned to at randomisation. Mis-randomised subjects (mis-randomised in IRT) and subjects with serious GCP violation at their site were excluded from FAS. If the actual stratum was different to the assigned stratum in IRT, the actual stratum was used in analyses.

In practice, in both studies M2301 and M2302, Randomised analysis set, and Full analyses set were the same.

Primary efficacy endpoint HISCR50 response

The primary clinical question of interest was: what is the effect of secukinumab vs. placebo on HiSCR50 response at Week 16 in subjects with moderate to severe hidradenitis suppurativa who were on the randomized study treatment.

The primary estimand was described by the following attributes:

- Population: Subjects with moderate to severe hidradenitis suppurativa who had a total of at least 5 inflammatory lesions, i.e., abscesses and/or inflammatory nodules, affecting at least 2 distinct anatomic areas, and who had HS diagnosed $\geq$1 years defined through appropriate inclusion/exclusion criteria.
- Endpoint: HiSCR50 response at Week 16, which was defined as at least a 50% decrease in abscess and inflammatory nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae from baseline to Week 16.
- Treatment of interest: The randomized study treatment (secukinumab 300 mg in two different dosing regimens Q2W and Q4W or placebo).
- The summary measure: odds ratio of secukinumab dose regimens vs. placebo.

The primary endpoint of the study was HiSCR50 response after 16 weeks of treatment. The statistical hypothesis for the primary endpoint being tested was that there was no difference in the proportion of HiSCR50 (HiSCR) responders at Week 16 in any of the secukinumab regimens versus placebo.

Let p_j denote the proportion of HiSCR50 response at Week 16 for treatment regimens j, j = 0, 1, 2 where

- 0 corresponds to placebo regimen
- 1 corresponds to secukinumab 300 mg Q2W s.c.
- 2 corresponds to secukinumab 300 mg Q4W s.c.

H_j: $p_j = p_0$ for j=1,2, was tested against the alternative H_{Aj} : $p_j \neq p_0$ for at least one secukinumab regimen, i.e.:

- H_1: secukinumab 300 mg Q2W s.c. is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment
- H_2: secukinumab 300 mg Q4W s.c. is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment.

The primary analysis method was logistic regression with treatment group, Hurley stage, and baseline AN count as explanatory variables. Geographical region, use of antibiotics and baseline body weight were also used as explanatory variables. Odds ratios were computed for comparisons of secukinumab dose regimens versus placebo utilizing the logistic regression model fit. Efficacy of two secukinumab regimens

compared to placebo with respect to HiSCR after 16 weeks of treatment was to be demonstrated if H_1 and/or H_2 is/are rejected in favour of secukinumab. In protocol amendment 2, the alpha level was reallocated as α=0.02 for secukinumab Q2W vs. placebo and α=0.005 for Q4W vs. placebo).

The pooled analysis of the two studies was similar to the primary analysis of individual studies except that study effect was added as an explanatory variable.

Handling of missing values/censoring/discontinuations

Missing data were multiple imputed based on the estimand strategy related to intercurrent events (ICE) or missing at random assumption for all missing values not related to intercurrent events. The following intercurrent events were considered:

1. Intake of prohibited medication/treatment (medication/treatment with possible confounding effect defined as biologics if taken more than once, antibiotics in the nonantibiotic stratum if taken over a period of more than 14 days, or any major HS-related surgery for HS other than allowed as a rescue therapy). A treatment policy strategy was applied in any case of prohibited medication. Such events were ignored, and all observed values were considered. Missing data was multiple imputed using a reference-based approach for the secukinumab groups and based on missing at random assumption for the placebo arm.
2. Intake of rescue medication: a composite strategy was applied. If such an event (intake of rescue antibiotics) occurred, the subject was considered as a non-responder.
3. Permanent discontinuation of study treatment due to adverse events or lack of efficacy: a composite strategy was applied in the same way as described under intercurrent event #2.
4. Permanent discontinuation of study treatment due to reasons other than adverse events or lack of efficacy: a hypothetical strategy was applied. Any observation after such an event was discarded and imputed via multiple imputation under the MAR assumption.
5. COVID-19 related intercurrent events:
    - missed at least one dose prior to Week 16 due to COVID-19;
    - discontinued treatment prior to Week 16 due to COVID-19.

   A treatment policy strategy was applied in the same way as described under intercurrent event #1.

Further justification of the ICE strategy is provided in the SAP (Amendment 4) but included for brevity.

As the primary endpoint in this study was a binary outcome derived from underlying quantitative variables, the imputations were performed on those continuous variables. In this analysis, the number of abscesses, inflammatory nodules, and draining fistulae were imputed separately and the response variable were derived based on the imputed values.

Sensitivity and supplementary analyses

Sensitivity analyses

A tipping point analysis in regard to the multiple imputation procedure was implemented.

Additionally, a sensitivity analysis considering a weighted baseline lesion count (weighted average of the screening and the baseline visits) was done.

Supplementary analysis

A supplementary estimand was implemented in which all attributes of this estimand remained the same as defined for the primary estimand apart from the handing of the intercurrent events: essentially all

intercurrent events were handled as per treatment policy strategy. Missing data were multiple imputed using a reference-based approach for the secukinumab arms and based on missing at random (MAR) assumption for the placebo arm.

Analysis supporting secondary objectives

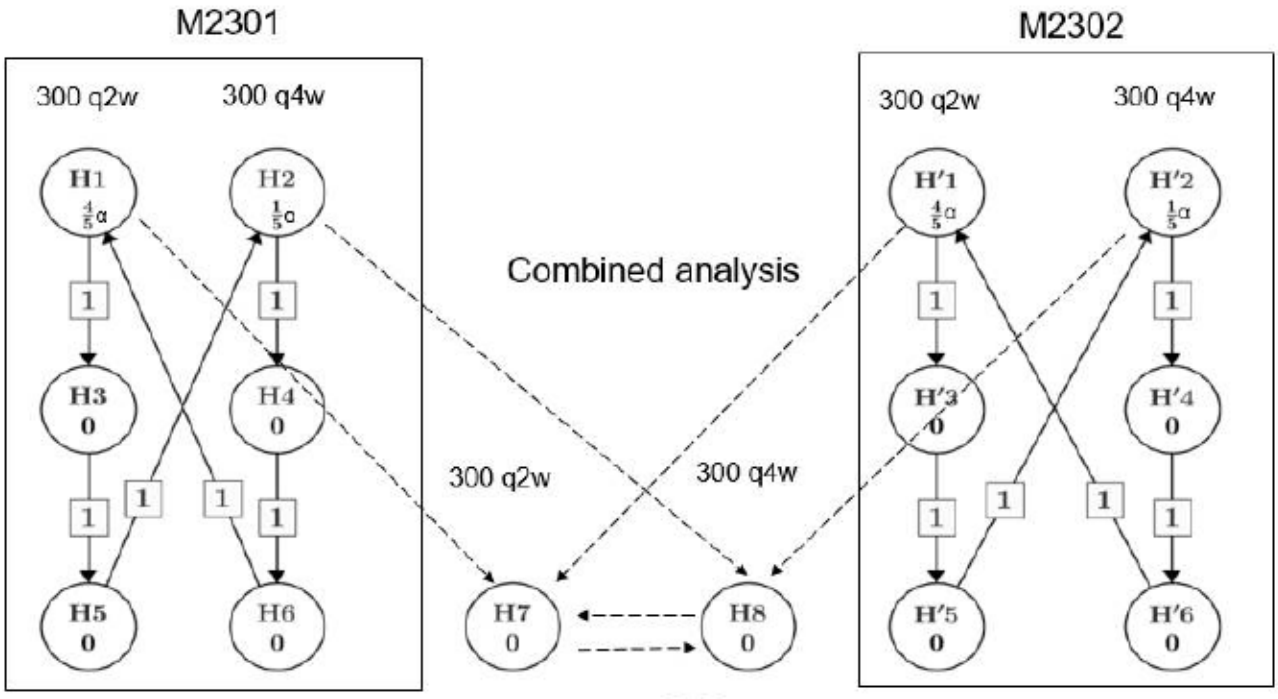
The analysis method for percentage change from baseline in AN count at Week 16 was an ANCOVA model with treatment group, Hurley stage, baseline AN counts, geographical region, use of antibiotic, and baseline body weight as explanatory variables.

The analysis method for the other two secondary endpoints will be logistic regression:

- Flare over 16 weeks: with treatment group, Hurley stage, and baseline AN counts as explanatory variables; geographical region, use of antibiotic, and baseline body weight (categorized as stratified) will be also included as explanatory variables.
- Skin Pain/NRS30 at Week 16: with treatment group, Hurley stage, and baseline NRS as explanatory variables; geographical region, use of antibiotic, baseline body weight (categorized as stratified), and study will be also included as explanatory variables. The data of both studies will be pooled for this analysis.

The MAH had prespecified a testing strategy for efficacy hypothesis across the primary and secondary endpoints, dose regimen and the two studies (**Figure 15**). Once HiSCR, percentage change in AN count and flare hypotheses for a secukinumab regimen were rejected, the respective 4α/5 for the Q2W regimen and α/5 for the Q4W regimen could be passed on to the other regimen's hypotheses, if they were not already rejected at the initial significance level. If both studies independently rejected the primary null-hypothesis on the same secukinumab regimen (H1 and H'1, or H2 and H'2), then the corresponding secukinumab regimen's pain hypothesis (H7 or H8) could be tested. Additionally, the significance level for a rejected pain hypothesis could be passed from one dose regimen to the other dose regimen and the primary null hypothesis on the two secukinumab regimen were all rejected. The initial significance level for pain hypothesis (H7 and/or H8) was set to $\alpha-\alpha^2$. The subtraction of α^2 was to account for the maximum possible type I error to claim a success for HiSCR, percentage change in AN count and flare in both studies. Therefore, the type I error rate was controlled at level α for the submission on all hypothesis endpoints. Under the global null hypothesis (i.e., no difference between secukinumab and placebo), the testing procedure outlined above controls the type I error rate (one-sided) at the study-level to <0.025, and at the submission level to <0.000625 ($=0.025^2$). Considering all possible configurations of true and false null hypotheses, the type I error control at the level of the submission is <0.000625 for the primary objectives, and <0.025 for all hypotheses.

Figure 15 Hypothesis testing strategy



Testing procedure and type-I-error control in the planned submission which consists of studies M2301 and M2302 (both with identical design). Hypotheses were only be tested in the order as indicated by the arrows.
Null hypotheses for Q2W vs. placebo and Q4W vs. placebo in M2301: H1 and H2, HiSCR at week 16; H3 and H4, percentage change from baseline in AN count at week 16; H5 and H6, flare over 16 weeks. H' denote the corresponding null hypotheses in M2302. H7 and H8: NRS30 at week 16 in M2301 and M2302 combined.

The long-term data, provided in response to the RSI, were mainly summarised in terms of observed case. In addition, HiSCR50 response was analysed with a mixed effects logistic regression model (MELRM) with treatment group, baseline AN count, visit, and treatment group*visit as fixed effects and with unstructured covariance matrix. Cumulative flares was analyses with a similar model but with AR(1) covariance matrix. Percentage change in AN count was analyses with a MMRM with the same set of fixed effects and applying unstructured covariance matrix. Time to flare distribution was estimated using the Kaplan-Meier method; subjects who did not experience a disease flare, were censored at the date of their last non-missing visit.

Interim analysis for futility or early efficacy

An interim analysis was planned when approximately 40% of the subjects in studies M2301 and M2302 combined have completed Week 16. The results were to be used to allow stopping the studies for demonstrated efficacy, or for futility.

Efficacy would be demonstrated, and the studies may validly be stopped as a result, if the following are satisfied for at least one of the secukinumab regimens: the difference between observed response rates for pooled data from both studies versus placebo exceeds 40%; and the difference between observed response rates on the corresponding secukinumab regimen vs. placebo exceeds 35% in both studies and is significant at a one-sided alpha level of 0.00001 (Haybittle-Peto type boundary). As a result, final analysis for each secukinumab regimen would be tested at one-sided adjusted alpha level of 0.01249.

Further details were provided in DMC Charter and Statistical Analysis Plan.

Results

Participant flow

Treatment Period 1

A total of 1084 subjects, 541 subjects in M2301 and 543 subjects in M2302, were randomised to secukinumab Q2W, secukinumab Q4W, placebo to secukinumab Q2W or placebo to secukinumab Q4W arms. Most subjects (94.1% in M2301 and 93.2% in M2302) completed the first 16 weeks of the study treatment (Treatment Period 1) in both studies. The subjects who discontinued the study treatment (5.9% in M2301 and 6.8% in M2302) also discontinued the study. Overall, the most frequently reported reason for discontinuing study treatment was subject decision in both studies (3.3% in M2301 and 3.7% in M2302). Discontinuation of study treatment due to adverse events was 0.9% in M2301 and 1.7% in M2302. Two subjects (one each in the secukinumab Q2W dose regimen and placebo) in M2302 discontinued study treatment due to lack of efficacy; it should however be noted that also for many discontinuations formally recorded as being due to subject decision, the reason is further specified as lack of efficacy. Subject disposition for Treatment Period 1 is summarised in **Table 5**.

Table 5 Subject disposition – Treatment Period 1 (M2301, M2302 and pooled data) (Randomised analysis set)

	M2301					M2302				
Disposition/Reason	**AIN457 Q2W**	**AIN457 Q4W**	**Any AIN457**	**PBO**	**Total**	**AIN457 Q2W**	**AIN457 Q4W**	**Any AIN457**	**PBO**	**Total**
	N=181	**N=180**	**N=361**	**N=180**	**N=541**	**N=180**	**N=180**	**N=360**	**N=183**	**N=543**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Completed Treatment Period 1	168 (92.8)	169 (93.9)	337 (93.4)	172 (95.6)	509 (94.1)	170 (94.4)	169 (93.9)	339 (94.2)	167 (91.3)	506 (93.2)
Discontinued Treatment	13 (7.2)	11 (6.1)	24 (6.6)	8 (4.4)	32 (5.9)	10 (5.6)	11 (6.1)	21 (5.8)	16 (8.7)	37 (6.8)
Primary reason for treatment discontinuation										
Adverse event	4 (2.2)	0 (0.0)	4 (1.1)	1 (0.6)	5 (0.9)	1 (0.6)	4 (2.2)	5 (1.4)	4 (2.2)	9 (1.7)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**1 (0.3)**	**1 (0.5)**	**2 (0.4)**
Lost to follow-up	3 (1.7)	1 (0.6)	4 (1.1)	1 (0.6)	5 (0.9)	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.5)	3 (0.6)
Physician decision	1 (0.6)	1 (0.6)	2 (0.6)	1 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	1 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)	1 (0.6)	0 (0.0)	1 (0.3)	1 (0.5)	2 (0.4)
Subject decision	4 (2.2)	9 (5.0)	13 (3.6)	5 (2.8)	18 (3.3)	6 (3.3)	6 (3.3)	12 (3.3)	8 (4.4)	20 (3.7)
- Logistics (moved/work/holiday/not available)	2 (1.1)	2 (1.1)	4 (1.1)	1 (0.6)	5 (0.9)	1 (0.6)	3 (1.7)	4 (1.1)	1 (0.5)	5 (0.9)
- Subject wish/personal reasons	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	4 (0.7)	1 (0.6)	0 (0.0)	1 (0.3)	2 (1.1)	3 (0.5)
- **Unsatisfactory treatment effect**	**2 (1.1)**	**2 (1.1)**	**4 (1.1)**	**0 (0.0)**	**4 (0.7)**	**1 (0.6)**	**1 (0.6)**	**2 (0.6)**	**1 (0.5)**	**3 (0.5)**
- Due to COVID-19	0 (0.0)	2 (1.1)	2 (0.6)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.6)	1 (0.3)	1 (0.5)	2 (0.4)
- Withdrawal of ICF	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.4)	3 (1.7)	0 (0.0)	3 (0.8)	1 (0.5)	4 (0.7)
- Adverse event	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	1 (0.2)
- Pregnancy wish	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
- Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)

N = Number of subjects randomized.

All percentages were computed using N as denominator.

M2301: Three subjects were excluded from randomized set: one subject each mis-randomized in IRT, one with serious GCP violation and one with a serious breach were excluded from the randomized set per SAP.

M2302: One subject mis-randomized in IRT is excluded from the randomized analysis set per analysis plan.

Source: [Study M2301 Week 16 CSR Table 14.1-1.2], [Study M2302 Week 16 CSR Table 14.1-1.2]

Entire study period

In studies M2301 and M2302, 76.0% and 77.2% of subjects, respectively, completed 52 weeks of study treatment. Among subjects who discontinued study treatment, the most frequently reported primary reason for discontinuing study treatment was subject decision in both studies (14.8% in M2301 and 12.5% in M2302). The proportion of subjects who discontinued study treatment due to adverse events was 3.5% in M2301 and 3.9% in M2302; for lack of efficacy, the proportions were 1.1% in M2301 and 2.0% in M2302. However, as already noted above, the predominant reason for the subject decision was unsatisfactory treatment effect in both studies (7.0% in M2301 and 4.1% in M2302).

Approximately 85% of subjects who completed the studies M2301 (340 out of 399) and M2302 (358 out of 418) entered the extension study. Subject disposition for the entire study period as of the data cut-off is summarised in **Table 6**.

Table 6 Subject disposition– Entire Study Period

	M2301					M2302				
Disposition/ Reason	AIN457 Q2W	AIN457 Q4W	PBO-AIN457 Q2W	PBO-AIN457 Q4W	Total	AIN457 Q2W	AIN457 Q4W	PBO-AIN457 Q2W	PBO-AIN457 Q4W	Total
	N=181	N=180	N=90	N=90	N=541	N=180	N=180	N=90	N=93	N=543
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed Treatment (Week 52)	131 (72.4)	137 (76.1)	68 (75.6)	75 (83.3)	411 (76.0)	149 (82.8)	133 (73.9)	68 (75.6)	69 (74.2)	419 (77.2)
Discontinued Treatment	50 (27.6)	43 (23.9)	22 (24.4)	15 (16.7)	130 (24.0)	31 (17.2)	47 (26.1)	22 (24.4)	24 (25.8)	124 (22.8)
Primary reason for treatment discontinuation										
Adverse event	10 (5.5)	5 (2.8)	2 (2.2)	2 (2.2)	19 (3.5)	7 (3.9)	7 (3.9)	4 (4.4)	3 (3.2)	21 (3.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Lack of efficacy	1 (0.6)	2 (1.1)	2 (1.1)	1 (0.6)	6 (1.1)	4 (2.2)	3 (1.7)	2 (2.2)	2 (2.2)	11 (2.0)
Lost to follow-up	6 (3.3)	4 (2.2)	3 (3.3)	2 (2.2)	15 (2.8)	2 (1.1)	9 (5.0)	1 (1.1)	1 (1.1)	13 (2.4)
Physician decision	1 (0.6)	3 (1.7)	1 (1.1)	2 (2.2)	7 (1.3)	1 (0.6)	2 (1.1)	0 (0.0)	2 (2.2)	5 (0.9)
Pregnancy	1 (0.6)	0 (0.0)	1 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.6)	1 (1.1)	0 (0.0)	2 (0.4)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study terminated by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Technical problems	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)	3 (0.6)
Subject decision	30 (16.6)	29 (16.1)	13 (14.4)	8 (8.9)	80 (14.8)	15 (8.3)	24 (13.3)	13 (14.4)	16 (17.2)	68 (12.5)
- Logistics (moved/work/ holiday/not available)	2 (1.1)	6 (3.3)	1 (1.1)	0 (0.0)	9 (1.7)	2 (1.1)	5 (2.8)	1 (1.1)	1 (1.1)	9 (1.7)
- Subject wish/personal reasons	7 (3.9)	2 (1.1)	5 (5.6)	3 (3.3)	17 (3.1)	1 (0.6)	5 (2.8)	3 (3.3)	5 (5.4)	14 (2.6)
- Unsatisfactory treatment effect	16 (8.8)	14 (7.8)	5 (5.6)	3 (3.3)	38 (7.0)	6 (3.3)	7 (3.9)	4 (4.4)	5 (5.4)	22 (4.1)
- Due to COVID-19	1 (0.6)	5 (2.8)	0 (0.0)	0 (0.0)	6 (1.1)	2 (1.1)	2 (1.1)	3 (3.3)	1 (1.1)	8 (0.7)
- Withdrawal of ICF	1 (0.6)	0 (0.0)	1 (1.1)	2 (2.2)	4 (0.7)	4 (2.2)	2 (1.1)	0 (0.0)	2 (2.2)	8 (0.7)
- Adverse event	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.6)	0 (0.0)	1 (1.1)	2 (0.4)

Table 7 Subject disposition – Entire Study Period

- Pregnancy wish	1 (0.6)	0 (0.0)	1 (1.1)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)
- Other	2 (1.1)	1 (0.6)	0 (0.0)	0 (0.0)	3 (0.6)	0 (0.0)	2 (1.1)	2 (2.2)	0 (0.0)	4 (0.7)

Source: [Appendix 2 Study M2301 Table 14.1-1.3, Listing 14.1-9.1], [Appendix 2 Study M2302 Table 14.1-1.3, Listing 14.1-9.1]

Recruitment

Study M2301 was conducted across 111 Investigator sites in 29 countries: Argentina (n=9), Australia (n=18), Austria (n=8), Belgium (n=10), Bulgaria (n=8), Canada (n=16), Czech Republic (n=18), France (n=56), Germany (n=64), Greece (n=19), Hungary (n=8), India (n=11), Israel (n=6), Italy (n=10), Japan (n=22), Mexico (n=8), Philippines (n=8), Poland (n=12), Portugal (n=26), Republic of Korea (n=9), Russia (n=17), Slovakia (n=8), Spain (n=27), Sweden (n=1), Switzerland (n=11), Taiwan (n=14), Turkey (n=9), United Kingdom (n=26) and United States (n=84).

Study M2032 was conducted across 108 Investigator sites in 32 countries: Argentina (n=14), Belgium (n=7), Bulgaria (n=10), Canada (n=14), Colombia (n=10), Croatia (n=2), Czech Republic (n=7), Denmark (n=10), France (n=71), Germany (n=68), Greece (n=13), Guatemala (n=11), Hungary (n=11), India (n=6), Israel (n=9), Italy (n=14), Lebanon (n=4), Lithuania (n=10), Malaysia (n=15), Netherlands (n=5), Philippines (n=3), Poland (n=22), Russia (n=15), Singapore (n=9), Slovakia (n=8), South Africa (n=21), Spain (n=27), Switzerland (n=7), Turkey (n=14), United Kingdom (n=20), United States (n=81) and Vietnam (n=5).

Conduct of the study

The original protocols for both studies had an effective date of 07 August 2018. First subject first visits took place on 31 January 2019 for M2301, and on 25 February 2019 for M2302. Data cut-offs for the Week 16 analyses took place on 01 October 2021 for M2301, and on 23 September 2021 for M2302.

The protocols were simultaneously amended on two occasions:

- In Amendment 01, dated 17 June 2020, corrective measures to address the emerging COVID-19 pandemic were implemented, including the potential for shipping study drug for home administration, remote visits and up to 3 unscheduled visits, and permitting the enrolment of up to 15% additional subjects if missing data due to COVID-19 jeopardises the pre-planned statistical power.
- In Amendment 02, dated 08 January 2021, the statistical testing strategy was amended to address emerging external data from a psoriasis study, which showed that a Q2W regimen could be preferable to Q4W in patients with a body weight of 90 kg or above. The split of the overall alpha level was thereby adjusted, allocating 80% to testing the Q2W regimen versus placebo. A secondary endpoint evaluating only the abscesses and inflammatory nodules (AN) count (AN count) was added. Furthermore, evaluation of inflammatory markers (ESR and CRP) and of the achievement of HiSCR in bio-naïve patients, and in patients with body weight lower and higher than 90 kg (<90 kg and ≥90 kg) were added as exploratory subgroup analyses. To address the ongoing pandemic, the respective sample sizes were also formally increased as already envisioned in Amendment 01.

In study M2301, 173 (32%) subjects had at least one protocol deviation during Treatment Period 1 (**Table 8**). The most common categories of protocol deviations were "treatment deviation" (18.1%), mainly related to home vs. site drug administration, "other" (10.5%), and "prohibited concomitant medication" (7.0%). **Table 9** shows protocol deviations in M2301 over the entire study period.

Table 8 Protocol deviations by deviation category in M2301 – Treatment Period 1 (Randomized set)

Protocol Deviation	AIN457 Q2W N=181 n (%)	AIN457 Q4W N=180 n (%)	Any AIN457 N=361 n (%)	Placebo N=180 n (%)	Total N=541 n (%)
Subjects with at least one protocol deviation	59 (32.6)	53 (29.4)	112 (31.0)	61 (33.9)	173 (32.0)
Selection criteria not met	8 (4.4)	8 (4.4)	16 (4.4)	4 (2.2)	20 (3.7)
Subject not withdrawn as per protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment deviation	33 (18.2)	27 (15.0)	60 (16.6)	38 (21.1)	98 (18.1)
Prohibited concomitant medication	12 (6.6)	12 (6.7)	24 (6.6)	14 (7.8)	38 (7.0)
Other*	20 (11.0)	18 (10.0)	38 (10.5)	19 (10.6)	57 (10.5)

- A subject with multiple occurrences of a protocol deviation category was counted only once in the protocol deviation category.
*Category "Other" covers PDs that do not fall into the previous categories (selection criteria not met, subject withdrawal as per protocol, treatment deviation or prohibited concomitant medication) and impact the completeness, accuracy, and/or reliability of study data or subject's rights, safety, and well-being; e.g., procedure was performed after the subject withdrew consent, GCP non-compliance of study site, or missed primary endpoint assessment.
- Subjects may have protocol deviations in more than one protocol deviation category.
Source: Table 14.1-2.1

Table 9 Protocol deviations by deviation category in M2301 – Entire study period (Randomized set)

Protocol Deviation	AIN457 Q2W N=181 n (%)	AIN457 Q4W N=180 n (%)	Any AIN457 Q2W N=266 n (%)	Any AIN457 Q4W N=267 n (%)	Any AIN457 N=533 n (%)
Subjects with at least one protocol deviation	100 (55.2)	94 (52.2)	129 (48.5)	129 (48.3)	258 (48.4)
Selection criteria not met	9 (5.0)	9 (5.0)	10 (3.8)	9 (3.4)	19 (3.6)
Subject not withdrawn as per protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment deviation	73 (40.3)	67 (37.2)	96 (36.1)	96 (36.0)	192 (36.0)
Prohibited concomitant medication	20 (11.0)	20 (11.1)	24 (9.0)	24 (9.0)	48 (9.0)
Other*	33 (18.2)	27 (15.0)	40 (15.0)	31 (11.6)	71 (13.3)

- A subject with multiple occurrences of a protocol deviation category was counted only once in the protocol deviation category.
*Category "Other" covers PDs that do not fall into the previous categories (selection criteria not met, subject withdrawal as per protocol, treatment deviation or prohibited concomitant medication) and impact the completeness, accuracy, and/or reliability of study data or subject's rights, safety, and well-being; e.g., procedure was performed after the subject withdrew consent, GCP non-compliance of study site, or missed primary endpoint assessment.
- Subjects may have protocol deviations in more than one protocol deviation category.
Source: Table 14.1-2.2

In study M2302, 158 (29.1%) subjects had at least one protocol deviation during Treatment Period 1 (**Table 10**). The most common categories of protocol deviations were "treatment deviation", mainly related to home vs. site drug administration (15.3%) and similar across groups, "other" (7.9%), and "prohibited concomitant medication" (7.6%). **Table 11** shows protocol deviations in M2302 over the entire study period.

Table 10 Protocol deviations by deviation category in M2302 - Treatment Period 1 (Randomized set)

Protocol deviation	AIN457 Q2W N=180 n (%)	AIN457 Q4W N=180 n (%)	Any AIN457 N=360 n (%)	Placebo N=183 n (%)	Total N=543 n (%)
Subjects with at least one protocol deviation	48 (26.7)	49 (27.2)	97 (26.9)	61 (33.3)	158 (29.1)
Selection criteria not met	8 (4.4)	13 (7.2)	21 (5.8)	8 (4.4)	29 (5.3)
Subject not withdrawn as per protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment deviation	23 (12.8)	29 (16.1)	52 (14.4)	31 (16.9)	83 (15.3)
Prohibited concomitant medication	14 (7.8)	7 (3.9)	21 (5.8)	20 (10.9)	41 (7.6)
Other*	15 (8.3)	11 (6.1)	26 (7.2)	17 (9.3)	43 (7.9)

- A subject with multiple occurrences of a protocol deviation category was counted only once in the protocol deviation category.
- Subjects may have protocol deviations in more than one protocol deviation category.
*Category "Other" covers PDs that do not fall into the previous categories (selection criteria not met, subject withdrawal as per protocol, treatment deviation or prohibited concomitant medication) and impact the completeness, accuracy, and/or reliability of study data or subject's rights, safety, and well-being; e.g., procedure was performed after the subject withdrew consent, GCP non-compliance of study site, or missed primary endpoint assessment.
Source: Table 14.1-2.1.

Table 11 Protocol deviations by deviation category in M2302 – Entire study period (Randomized set)

Protocol deviation	AIN457 Q2W N=180 n (%)	AIN457 Q4W N=180 n (%)	Any AIN457 Q2W N=261 n (%)	Any AIN457 Q4W N=266 n (%)	Any AIN457 N=527 n (%)
Subjects with at least one protocol deviation	102 (56.7)	93 (51.7)	137 (52.5)	127 (47.7)	264 (50.1)
Selection criteria not met	8 (4.4)	13 (7.2)	8 (3.1)	13 (4.9)	21 (4.0)
Subject not withdrawn as per protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment deviation	77 (42.8)	73 (40.6)	105 (40.2)	103 (38.7)	208 (39.5)
Prohibited concomitant medication	23 (12.8)	15 (8.3)	28 (10.7)	19 (7.1)	47 (8.9)
Other*	24 (13.3)	18 (10.0)	32 (12.3)	21 (7.9)	53 (10.1)

- A subject with multiple occurrences of a protocol deviation category was counted only once in the protocol deviation category.
- Subjects may have protocol deviations in more than one protocol deviation category.
*Category "Other" covers PDs that do not fall into the previous categories (selection criteria not met, subject withdrawal as per protocol, treatment deviation or prohibited concomitant medication) and impact the completeness, accuracy, and/or reliability of study data or subject's rights, safety, and well-being; e.g., procedure was performed after the subject withdrew consent, GCP non-compliance of study site, or missed primary endpoint assessment.
Source: Table 14.1-2.2.

Baseline data

Overall, the mean age of subjects was 36.1 years in M2301 and 36.3 years in M2302 with the majority of the subjects aged between 30 and <65 years in both studies. In M2301, the proportion of subjects <30 years was slightly higher in the secukinumab Q4W dose regimen compared to the other treatment groups (32.0% in Q2W, 38.3% in Q4W, 28.3% in placebo) while in M2302, the proportion of subjects aged 40 to <65 was higher in the secukinumab Q2W dose regimen compared to the other treatment groups (42.8% in Q2W, 31.7% in Q4W, 32.2% in placebo). The proportion of female subjects was 56.2% in M2301 and 56.4% in M2302 and the proportion of White subjects was 79.5% in M2301 and 76.4% in M2302. The mean BMI was 32.46 kg/m^2 in M2301 and 31.76 kg/m^2 in M2302. The proportion of subjects weighing ≥ 90 kg was 54.7% in M2301 and 50.8% in M2302. More than half of the subjects were current smokers in both studies (54.0% each). The proportion of never smokers in M2301 was slightly higher in the secukinumab Q2W (33.1%) and Q4W (31.1%) dose regimens compared to placebo (27.2%) and that proportion in M2302 was higher in secukinumab Q4W dose regimen (36.1%) compared to secukinumab Q2W dose regimen (28.3%) and placebo (29.0%). A summary of demographic characteristics is displayed in **Table 12**.

Table 12 Demographic characteristics (M2301, M2302 and pooled data) (Randomized analysis set)

	M2301				M2302				Pooled data			
Characteristic	AIN457 Q2W N=181	AIN457 Q4W N=180	Placebo N=180	Total N=541	AIN457 Q2W N=180	AIN457 Q4W N=180	Placebo N=183	Total N=543	AIN457 Q2W N=361	AIN457 Q4W N=360	Placebo N=363	Total N=1084
Age group in years, n (%)												
< 30	58 (32.0)	69 (38.3)	51 (28.3)	178 (32.9)	52 (28.9)	60 (33.3)	57 (31.1)	169 (31.1)	110 (30.5)	129 (35.8)	108 (29.8)	347 (32.0)
30-<40	56 (30.9)	45 (25.0)	70 (38.9)	171 (31.6)	48 (26.7)	61 (33.9)	65 (35.5)	174 (32.0)	104 (28.8)	106 (29.4)	135 (37.2)	345 (31.8)
40-<65	64 (35.4)	63 (35.0)	58 (32.2)	185 (34.2)	77 (42.8)	57 (31.7)	59 (32.2)	193 (35.5)	141 (39.1)	120 (33.3)	117 (32.2)	378 (34.9)
≥65	3 (1.7)	3 (1.7)	1 (0.6)	7 (1.3)	3 (1.7)	2 (1.1)	2 (1.1)	7 (1.3)	6 (1.7)	5 (1.4)	3 (0.8)	14 (1.3)
Age (years)												
Mean (SD)	37.1 (12.53)	35.7 (11.71)	35.5 (10.75)	36.1 (11.69)	37.3 (11.48)	35.5 (11.41)	36.2 (11.25)	36.3 (11.38)	37.2 (12.00)	35.6 (11.55)	35.9 (10.99)	36.2 (11.53)
Median (min-max)	35.0 (18-73)	34.0 (18-67)	33.5 (19-65)	34.0 (18-73)	37.0 (18-67)	33.5 (18-71)	34.0 (18-71)	35.0 (18-71)	36.0 (18-73)	34.0 (18-71)	34.0 (18-71)	34.0 (18-73)
Gender, n (%)												
Male	79 (43.6)	80 (44.4)	78 (43.3)	237 (43.8)	82 (45.6)	77 (42.8)	78 (42.6)	237 (43.6)	161 (44.6)	157 (43.6)	156 (43.0)	474 (43.7)
Female	102 (56.4)	100 (55.6)	102 (56.7)	304 (56.2)	98 (54.4)	103 (57.2)	105 (57.4)	306 (56.4)	200 (55.4)	203 (56.4)	207 (57.0)	610 (56.3)
Race, n (%)												
White	145 (80.1)	146 (81.1)	139 (77.2)	430 (79.5)	133 (73.9)	139 (77.2)	143 (78.1)	415 (76.4)	278 (77.0)	285 (79.2)	282 (77.7)	845 (78.0)
Black or African American	15 (8.3)	10 (5.6)	12 (6.7)	37 (6.8)	18 (10.0)	19 (10.6)	12 (6.6)	49 (9.0)	33 (9.1)	29 (8.1)	24 (6.6)	86 (7.9)
Asian	19 (10.5)	23 (12.8)	24 (13.3)	66 (12.2)	16 (8.9)	16 (8.9)	19 (10.4)	51 (9.4)	35 (9.7)	39 (10.8)	43 (11.8)	117 (10.8)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
American Indian or Alaska native	1 (0.6)	1 (0.6)	2 (1.1)	4 (0.7)	7 (3.9)	5 (2.8)	8 (4.4)	20 (3.7)	8 (2.2)	6 (1.7)	10 (2.8)	24 (2.2)
Multiple	1 (0.6)	0 (0.0)	3 (1.7)	4 (0.7)	4 (2.2)	1 (0.6)	1 (0.5)	6 (1.1)	5 (1.4)	1 (0.3)	4 (1.1)	10 (0.9)
Not Reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Ethnicity, n (%)												
Hispanic or Latino	18 (9.9)	21 (11.7)	22 (12.2)	61 (11.3)	35 (19.4)	30 (16.7)	33 (18.0)	98 (18.0)	53 (14.7)	51 (14.2)	55 (15.2)	159 (14.7)
Not Hispanic or Latino	157 (86.7)	152 (84.4)	157 (87.2)	466 (86.1)	136 (75.6)	144 (80.0)	143 (78.1)	423 (77.9)	293 (81.2)	296 (82.2)	300 (82.6)	889 (82.0)
Not Reported	4 (2.2)	6 (3.3)	0 (0.0)	10 (1.8)	8 (4.4)	6 (3.3)	7 (3.8)	21 (3.9)	12 (3.3)	12 (3.3)	7 (1.9)	31 (2.9)
Unknown	2 (1.1)	1 (0.6)	1 (0.6)	4 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.8)	1 (0.3)	1 (0.3)	5 (0.5)
Weight (kg)												
Mean (SD)	95.87 (25.032)	95.43 (25.894)	92.88 (22.098)	94.73 (24.387)	92.57 (24.308)	93.13 (22.271)	90.96 (22.020)	92.21 (22.861)	94.23 (24.695)	94.28 (24.144)	91.91 (22.049)	93.47 (23.658)
Median (min-max)	92.00 (51.0-205.0)	92.35 (43.0-201.6)	92.00 (47.4-159.2)	92.00 (43.0-205.0)	90.00 (50.0-181.9)	90.00 (50.0-152.0)	89.40 (49.8-157.0)	90.00 (49.8-181.9)	91.00 (50.0-205.0	91.00 (43.0-201.6)	91.00 (47.4-159.2)	91.00 (43.0-205.0)
Weight groups (kg), n (%)												
<90	82 (45.3)	80 (44.4)	83 (46.1)	245 (45.3)	86 (47.8)	89 (49.4)	92 (50.3)	267 (49.2)	168 (46.5)	169 (46.9)	175 (48.2)	512 (47.2)
≥90	99 (54.7)	100 (55.6)	97 (53.9)	296 (54.7)	94 (52.2)	91 (50.6)	91 (49.7)	276 (50.8)	193 (53.5)	191 (53.1)	188 (51.8)	572 (52.8)
BMI (kg/m²)												
n	181	179	180	540	180	180	183	543	361	359	363	1083
Mean (SD)	32.64 (7.904)	32.78 (7.897)	31.97 (7.053)	32.46 (7.622)	31.90 (7.788)	31.98 (7.478)	31.42 (7.382)	31.76 (7.540)	32.27 (7.844)	32.38 (7.690)	31.69 (7.216)	32.11 (7.586)
Median (min-max)	31.79 (14.7-59.0)	31.83 (18.3-61.8)	31.30 (16.8-51.3)	31.57 (14.7-61.8)	31.75 (16.9-64.3)	31.08 (19.3-56.9)	30.35 (18.2-52.2)	31.09 (16.9-64.3)	31.79 (14.7-64.3)	31.25 (18.3-61.8)	31.07 (16.8-52.2)	31.25 (14.7-64.3)
Smoking Status, n (%)												
Never	60 (33.1)	56 (31.1)	49 (27.2)	165 (30.5)	51 (28.3)	65 (36.1)	53 (29.0)	169 (31.1)	111 (30.7)	121 (33.6)	102 (28.1)	334 (30.8)
Current	95 (52.5)	96 (53.3)	101 (56.1)	292 (54.0)	97 (53.9)	90 (50.0)	106 (57.9)	293 (54.0)	192 (53.2)	186 (51.7)	207 (57.0)	585 (54.0)
Former	26 (14.4)	28 (15.6)	30 (16.7)	84 (15.5)	32 (17.8)	25 (13.9)	24 (13.1)	81 (14.9)	58 (16.1)	53 (14.7)	54 (14.9)	165 (15.2)

- Weight and height are taken from baseline visit.
- Race 'Multiple' means multiple entries are selected in the eCRF.

Source: [Study M2301-Table 14.1-5], [Study M2302-Table 14.1-5], [SCS Appendix 1-Table 1.3-1.1]

Mean time since HS diagnosis was 7.1 years in M2301 and 7.4 years in M2302, while the mean time since symptom-onset was 13.0 years in M2301 and 13.3 years in M2302. Most subjects presented with Hurley stage II or III at baseline (61.4% and 34.0% in M2301 and 56.7% and 40.5% in M2302, respectively). When the treatment groups were compared in each study, the proportion of subjects with Hurley stage III, which describes a more severe population with a greater component of scarring, fibrosis and tunnels, was higher in the secukinumab Q2W (38.7%) and Q4W (35.0%) dose regimens than in placebo (28.3%) in M2301, and was higher in the secukinumab Q2W dose regimen (45.6%) than in the secukinumab Q4W dose regimen (37.8%) and placebo (38.3%) in M2302.

Overall, the proportion of subjects with previous exposure to systemic biologic therapy was 23.8% in M2301 and 23.2% in M2302, and most of these subjects received adalimumab (22.6% in M2301, 21.4% in M2302). Most subjects received previous systemic antibiotics (82.3% in M2301, 83.6% in M2302), which had been mostly discontinued by the time of study entry for the predominant reason of lack of efficacy (approximately 60%). The proportion of subjects who had undergone surgical intervention for HS was 39.9% in M2301 and 41.6% in M2302. The proportion of subjects who entered the studies on a stable dose of systemic antibiotics was similar between the treatment groups in the individual studies: 14.4% in the secukinumab Q2W dose regimen, 13.9% in the secukinumab Q4W dose regimen, 10.0% in placebo in M2301; 10.0% in the secukinumab Q2W dose regimen, 11.7% in the secukinumab Q4W dose regimen, 10.4% in placebo in M2302.

Disease history and baseline disease characteristics are summarised in **Table 13**. According to the MAH, the secukinumab Q2W dose regimen in both studies comprised a more severe population (i.e., more subjects with Hurley stage III, having higher abscess and fistulae count) compared to the other treatment groups. This imbalance was prominent in M2302, and the overall population was more severe in M2302 than in M2301. Similar to the trends observed in the individual studies, the pooled secukinumab Q2W dose regimen also comprised a more severe population than the other pooled groups.

Table 13 Disease history and baseline disease characteristics (M2301, M2302 and pooled data) (Randomized analysis set)

	M2301				M2302				Pooled data			
Background characteristic	AIN457 Q2W N=181	AIN457 Q4W N=180	Placebo N=180	Total N=541	AIN457 Q2W N=180	AIN457 Q4W N=180	Placebo N=183	Total N=543	AIN457 Q2W N=361	AIN457 Q4W N=360	Placebo N=363	Total N=1084
Baseline Hurley stage, n (%)												
I	7 (3.9)	10 (5.6)	8 (4.4)	25 (4.6)	6 (3.3)	6 (3.3)	3 (1.6)	15 (2.8)	13 (3.6)	16 (4.4)	11 (3.0)	40 (3.7)
II	104 (57.5)	107 (59.4)	121 (67.2)	332 (61.4)	92 (51.1)	106 (58.9)	110 (60.1)	308 (56.7)	196 (54.3)	213 (59.2)	231 (63.6)	640 (59.0)
III	70 (38.7)	63 (35.0)	51 (28.3)	184 (34.0)	82 (45.6)	68 (37.8)	70 (38.3)	220 (40.5)	152 (42.1)	131 (36.4)	121 (33.3)	404 (37.3)
Family history of HS, n (%)												
Yes	35 (19.3)	52 (28.9)	55 (30.6)	142 (26.2)	39 (21.7)	42 (23.3)	41 (22.4)	122 (22.5)	74 (20.5)	94 (26.1)	96 (26.4)	264 (24.4)
No	146 (80.7)	128 (71.1)	125 (69.4)	399 (73.8)	141 (78.3)	138 (76.7)	142 (77.6)	421 (77.5)	287 (79.5)	266 (73.9)	267 (73.6)	820 (75.6)
Time since HS symptom(s) onset (years)												
Mean (SD)	13.4 (9.92)	13.1 (9.20)	12.6 (9.55)	13.0 (9.55)	13.3 (10.28)	13.7 (9.86)	13.0 (9.53)	13.3 (9.88)	13.3 (10.09)	13.4 (9.53)	12.8 (9.53)	13.2 (9.71)
Median (min-max)	10.5 (1-44)	10.3 (1-47)	10.2 (1-52)	10.3 (1-52)	11.4 (1-49)	10.9 (1-43)	10.5 (1-43)	11.0 (1-49)	11.1 (1-49)	10.7 (1-47)	10.3 (1-52)	10.6 (1-52)
Time since diagnosis of HS (years)												
n	181	180	180	541	180	180	182	542	361	360	362	1083
Mean (SD)	7.4 (7.98)	6.6 (6.73)	7.5 (7.00)	7.1 (7.25)	7.1 (7.04)	8.2 (8.42)	7.0 (6.65)	7.4 (7.41)	7.2 (7.52)	7.4 (7.65)	7.2 (6.82)	7.3 (7.33)
Median (min-max)	4.7 (0-42)	4.1 (0-44)	5.0 (1-39)	4.7 (0-44)	4.8 (0-47)	4.8 (1-43)	4.4 (0-31)	4.8 (0-47)	4.8 (0-47)	4.4 (0-44)	4.8 (0-39)	4.7 (0-47)
Baseline AN count												
Mean (SD)	12.9 (9.60)	12.6 (8.38)	12.8 (8.15)	12.8 (8.72)	13.9 (9.93)	13.3 (8.77)	12.8 (8.45)	13.3 (9.08)	13.4 (9.76)	12.9 (8.58)	12.8 (8.29)	13.0 (8.89)
Median (min-max)	10.0 (3-81)	10.0 (5-63)	10.0 (5-42)	10.0 (3-81)	11.0 (4-60)	11.0 (5-51)	10.0 (5-45)	11.0 (4-60)	10.0 (3-81)	10.0 (5-63)	10.0 (5-45)	10.0 (3-81)
Baseline inflammatory nodule count												
Mean (SD)	10.1 (7.80)	9.9 (7.60)	10.1 (6.99)	10.0 (7.46)	10.0 (7.71)	10.4 (7.60)	9.6 (6.77)	10.0 (7.36)	10.0 (7.75)	10.1 (7.60)	9.9 (6.87)	10.0 (7.41)
Median (min-max)	8.0 (0-53)	8.0 (0-62)	8.0 (1-36)	8.0 (0-62)	8.0 (0-50)	8.0 (0-43)	8.0 (0-41)	8.0 (0-50)	8.0 (0-53)	8.0 (0-62)	8.0 (0-41)	8.0 (0-62)
Baseline abscess count												
Mean (SD)	2.9 (4.26)	2.7 (3.98)	2.7 (3.76)	2.7 (3.99)	3.9 (5.41)	2.9 (4.13)	3.2 (4.96)	3.3 (4.87)	3.4 (4.89)	2.8 (4.04)	2.9 (4.41)	3.0 (4.46)
Median (min-max)	1.0 (0-30)	1.0 (0-31)	1.0 (0-21)	1.0 (0-31)	2.0 (0-45)	1.0 (0-26)	1.0 (0-32)	2.0 (0-45)	2.0 (0-45)	1.0 (0-31)	1.0 (0-32)	2.0 (0-45)
Baseline draining fistulae count												
Mean (SD)	2.9 (3.41)	2.5 (3.52)	2.4 (3.16)	2.6 (3.37)	3.0 (3.63)	2.5 (3.50)	2.6 (3.24)	2.7 (3.46)	2.9 (3.51)	2.5 (3.51)	2.5 (3.19)	2.6 (3.41)
Median (min-max)	2.0 (0-17)	1.0 (0-16)	1.0 (0-17)	1.0 (0-17)	2.0 (0-17)	1.0 (0-19)	2.0 (0-19)	1.0 (0-19)	2.0 (0-17)	1.0 (0-19)	1.0 (0-19)	1.0 (0-19)
Baseline total fistulae count												
Mean (SD)	5.3 (5.57)	4.4 (5.24)	4.7 (5.25)	4.8 (5.36)	5.1 (4.99)	4.7 (5.26)	4.6 (4.90)	4.8 (5.05)	5.2 (5.28)	4.5 (5.25)	4.7 (5.07)	4.8 (5.20)
Median (min-max)	4.0 (0-26)	2.0 (0-19)	3.0 (0-19)	3.0 (0-26)	4.0 (0-19)	2.5 (0-20)	3.0 (0-20)	3.0 (0-20)	4.0 (0-26)	2.0 (0-20)	3.0 (0-20)	3.0 (0-26)
Baseline NRS												
n	163	163	162	488	166	163	166	495	329	326	328	983
Mean (SD)	5.2 (2.51)	4.9 (2.53)	5.0 (2.61)	5.0 (2.55)	5.4 (2.42)	5.3 (2.46)	5.3 (2.48)	5.3 (2.45)	5.3 (2.47)	5.1 (2.50)	5.2 (2.54)	5.2 (2.50)
Median (min-max)	5.3 (0-10)	5.0 (0-10)	5.4 (0-10)	5.2 (0-10)	5.3 (0-10)	5.6 (0-10)	5.6 (0-10)	5.6 (0-10)	5.3 (0-10)	5.3 (0-10)	5.6 (0-10)	5.4 (0-10)
Baseline HS-PGA, n (%)												
0 = Clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 = Minimal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 = Mild	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)	1 (0.3)	1 (0.3)	2 (0.6)	4 (0.4)
3 = Moderate	90 (49.7)	96 (53.3)	91 (50.6)	277 (51.2)	74 (41.1)	85 (47.2)	91 (49.7)	250 (46.0)	164 (45.4)	181 (50.3)	182 (50.1)	527 (48.6)
4 = Severe	27 (14.9)	28 (15.6)	34 (18.9)	89 (16.5)	39 (21.7)	37 (20.6)	33 (18.0)	109 (20.1)	66 (18.3)	65 (18.1)	67 (18.5)	198 (18.3)
5 = Very severe	63 (34.8)	55 (30.6)	54 (30.0)	172 (31.8)	67 (37.2)	58 (32.2)	58 (31.7)	183 (33.7)	130 (36.0)	113 (31.4)	112 (30.9)	355 (32.7)
Baseline mHSS												
n	180	180	179	539	178	177	181	536	358	357	360	1075
Mean (SD)	57.4 (39.96)	53.4 (35.75)	49.2 (37.98)	53.3 (38.01)	58.3 (38.41)	51.1 (34.16)	51.7 (34.27)	53.7 (35.74)	57.8 (39.14)	52.3 (34.94)	50.4 (36.13)	53.5 (36.88)
Median (min-max)	43.5 (7-223)	40.5 (5-210)	37.0 (11-263)	40.0 (5-263)	46.0 (16-217)	40.0 (13-214)	41.0 (6-229)	43.0 (6-229)	45.0 (7-223)	40.0 (5-214)	40.0 (6-263)	42.0 (5-263)
Baseline DLQI total score												
n	164	151	163	478	161	168	175	504	325	319	338	982
Mean (SD)	14.2 (6.71)	13.4 (6.15)	13.8 (7.17)	13.8 (6.70)	15.7 (7.05)	14.6 (7.21)	14.5 (6.92)	14.9 (7.06)	14.9 (6.91)	14.1 (6.75)	14.2 (7.04)	14.4 (6.91)
Median (min-max)	14.0 (1-29)	13.0 (1-27)	13.0 (0-30)	13.0 (0-30)	15.0 (1-30)	15.0 (0-30)	13.0 (0-30)	15.0 (0-30)	15.0 (1-30)	14.0 (0-30)	13.0 (0-30)	14.0 (0-30)
Prior surgery for HS, n (%)												
Yes	71 (39.2)	73 (40.6)	72 (40.0)	216 (39.9)	78 (43.3)	70 (38.9)	78 (42.6)	226 (41.6)	149 (41.3)	143 (39.7)	150 (41.3)	442 (40.8)
No	110 (60.8)	107 (59.4)	108 (60.0)	325 (60.1)	102 (56.7)	110 (61.1)	105 (57.4)	317 (58.4)	212 (58.7)	217 (60.3)	213 (58.7)	642 (59.2)
Previous exposure to systemic biologic therapy, n (%)												
Yes	44 (24.3)	39 (21.7)	46 (25.6)	129 (23.8)	36 (20.0)	42 (23.3)	48 (26.2)	126 (23.2)	80 (22.2)	81 (22.5)	94 (25.9)	255 (23.5)

Table 13, cont'd Disease history and baseline disease characteristics (M2301, M2302 and pooled data) (Randomized analysis set)

	M2301				M2302				Pooled data			
Background characteristic	AIN457 Q2W N=181	AIN457 Q4W N=180	Placebo N=180	Total N=541	AIN457 Q2W N=180	AIN457 Q4W N=180	Placebo N=183	Total N=543	AIN457 Q2W N=361	AIN457 Q4W N=360	Placebo N=363	Total N=1084
No	137 (75.7)	141 (78.3)	134 (74.4)	412 (76.2)	144 (80.0)	138 (76.7)	135 (73.8)	417 (76.8)	281 (77.8)	279 (77.5)	269 (74.1)	829 (76.5)
Previous exposure to adalimumab, n (%)												
Yes	41 (22.7)	38 (21.1)	43 (23.9)	122 (22.6)	34 (18.9)	38 (21.1)	44 (24.0)	116 (21.4)	75 (20.8)	76 (21.1)	87 (24.0)	238 (22.0)
No	140 (77.3)	142 (78.9)	137 (76.1)	419 (77.4)	146 (81.1)	142 (78.9)	139 (76.0)	427 (78.6)	286 (79.2)	284 (78.9)	276 (76.0)	846 (78.0)
Previous exposure to systemic antibiotics, n (%)												
Yes	146 (80.7)	149 (82.8)	150 (83.3)	445 (82.3)	151 (83.9)	152 (84.4)	151 (82.5)	454 (83.6)	297 (82.3)	301 (83.6)	301 (82.9)	899 (82.9)
No	35 (19.3)	31 (17.2)	30 (16.7)	96 (17.7)	29 (16.1)	28 (15.6)	32 (17.5)	89 (16.4)	64 (17.7)	59 (16.4)	62 (17.1)	185 (17.1)
Previous exposure to non- biologic and non-antibiotic systemic therapy, n (%)												
Yes	64 (35.4)	66 (36.7)	62 (34.4)	192 (35.5)	63 (35.0)	54 (30.0)	62 (33.9)	179 (33.0)	127 (35.2)	120 (33.3)	124 (34.2)	371 (34.2)
No	117 (64.6)	114 (63.3)	118 (65.6)	349 (64.5)	117 (65.0)	126 (70.0)	121 (66.1)	364 (67.0)	234 (64.8)	240 (66.7)	239 (65.8)	713 (65.8)

Source: [Study M2301-Table 14.1-6 fix], [Study M2302-Table 14.1-6 fix], [SCS Appendix 1-Table 1.4-1.1 fix]

In pooled data for the overall population, the most frequently (≥5%) reported medical history or current medical conditions included hypertension (16.0%), depression (11.2%), obesity (9.1%), asthma (8.9%), seasonal allergy (7.4%), anxiety (7.3%), acne (7.2%), headache (7.2%), drug hypersensitivity (6.6%), migraine (6.2%), gastroesophageal reflux disease (5.5%), type 2 diabetes mellitus (5.4%) and hypothyroidism (5.1%).

Numbers analysed

Table 14 and **Table 15** display the Treatment Period 1 analysis sets for M2301 and M2302, respectively. As noted above, pain response was primarily analysed among subjects with baseline NRS ≥3 (total N=769, i.e., about 71% of the total number of subjects) and was only pre-planned to be analysed with pooled data.

Table 14 Analysis sets for M2301 – Treatment period 1 (All subjects enrolled)

Analysis population	AIN457 Q2W	AIN457 Q4W	Any AIN457	Placebo	Total
Randomized set (RAN)	181	180	361	180	541
Full analysis set (FAS)	181	180	361	180	541
Safety set (SAF)	181	180	361	180	541

- 3 subjects excluded from the randomized set due to the following reasons: 1 mis-randomization in IRT, 2 serious GCP violation.
Source: Table 14.1-4.1

Table 15 Analysis sets for M2302 – Treatment period 1 (All subjects enrolled)

Analysis population	AIN457 Q2W	AIN457 Q4W	Any AIN457	Placebo	Total
Randomized set	180	180	360	183	543
Full analysis set	180	180	360	183	543
Safety set	180	180	360	183	543

- One subject mis-randomized in IRT is excluded from the randomized analysis set per SAP.
Source: Table 14.1-4.1.

Outcomes and estimation

Within the MAH's testing strategy, M2301 met the primary and all secondary objectives and M2302 met the primary and all but one secondary objectives for the secukinumab Q2W dose regimen. The primary and all but one secondary objectives were met for the secukinumab Q4W dose regimen in M2302, whereas in M2301, hypothesis testing stopped at the primary endpoint with a nominal p-value of 0.0418. See **Table 16**.

Table 16 Results of hypothesis tests within testing strategy (M2301, M2302 and Pooled data) (Full analysis set)

Hypothesis	Endpoint	Comparison vs. Placebo	M2301		M2302	
			One-sided p-value	Outcome vs. Placebo	One-sided p-value	Outcome vs. Placebo
H1	HiSCR50 at Week 16	AIN457 Q2W	0.0070	Superior	0.0149	Superior
H2	HiSCR50 at Week 16	AIN457 Q4W	0.0418	Not superior	0.0022	Superior
H3	AN count at Week 16	AIN457 Q2W	<0.0001	Superior	0.0051	Superior
H4	AN count at Week 16	AIN457 Q4W	0.0004	Not superior	0.0001	Superior
H5	Flares over Week 16	AIN457 Q2W	0.0010	Superior	0.0732	Not superior
H6	Flares over Week 16	AIN457 Q4W	0.0926	Not superior	0.0049	Superior
			Pooled data			
			One-sided p-value	Outcome vs. Placebo		
H7	NRS30 at Week 16	AIN457 Q2W	0.0003	Superior		
H8	NRS30 at Week 16	AIN457 Q4W	0.0044	Not superior		

- One-sided nominal p-values are presented. The level of a rejected hypothesis is only passed on to next hypothesis (in the testing hierarchy), if the treatment effect is in favor of AIN457.
- H1, H3, H5 cover the high dose regimen (AIN457 Q2W) and are tested in a hierarchical order (initial one-sided significance level: 0.02).
- H2, H4, H6 cover the low dose regimen (AIN457 Q4W) and are tested in a hierarchical order (initial one-sided significance level: 0.005).
- H7 and H8 are based on pooled data from study M2301 and M2302 (initial one-sided significance levels of 0.019375 and 0.004375, respectively).

Source: [Study M2301-Table 14.2-6.1a fix], [Study M2302-Table 14.2-6.1a fix]

Primary endpoint – HiSCR50 response

In both studies, both secukinumab dose regimens showed higher HiSCR50 response rates than placebo at Week 16 (45.0% in secukinumab Q2W, 41.8% in secukinumab Q4W, 33.7% in placebo in M2301; 42.3% in secukinumab Q2W, 46.1% in secukinumab Q4W, 31.2% in placebo in M2302). The estimated odds ratio of secukinumab to placebo for HiSCR50 response rate at Week 16 was statistically significant for the secukinumab Q2W dose regimen in both studies. For the secukinumab Q4W dose regimen, statistical significance was shown only in study M2302, in which the treatment difference to placebo was even larger for the Q4W regimen than for the Q2W regimen (14.9 and 11.1 percentage points, respectively). Pooled data supported the treatment effect of both secukinumab doses. **Table 17** displays the results of the logistic regression analysis, and **Figure 16** displays the corresponding forest plot.

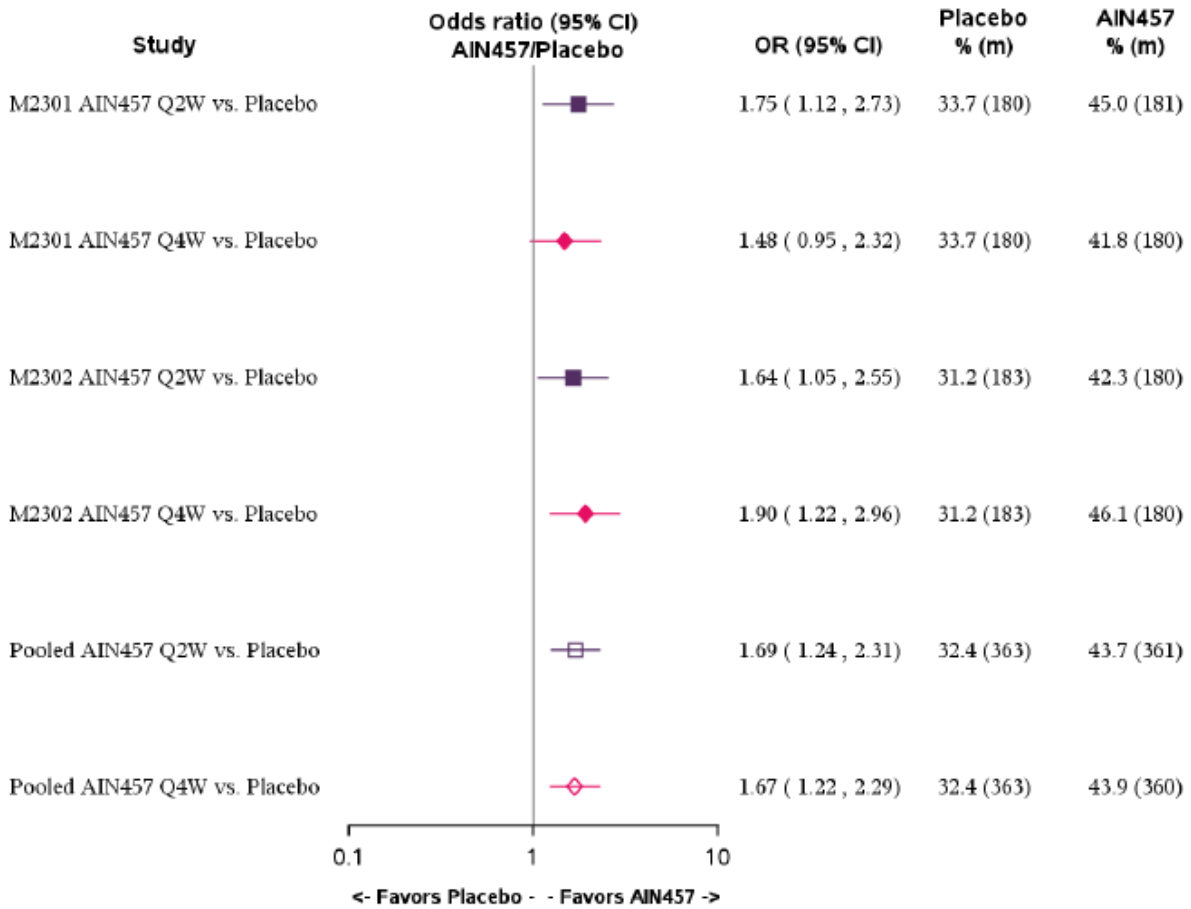
Table 17 Logistic regression analysis of HiSCR50 response at Week 16 (primary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)

Study No.	Treatment comparison "test" vs. "control"	"test" n*/m (%)	"control" n*/m (%)	odds ratio estimate (95%CI)	One-sided p-value
M2301	AIN457 Q2W vs. Placebo	81.5/181 (45.0)	60.7/180 (33.7)	1.75 (1.12, 2.73)	0.0070**
	AIN457 Q4W vs. Placebo	75.2/180 (41.8)	60.7/180 (33.7)	1.48 (0.95, 2.32)	0.0418
	AIN457 Q2W vs. AIN457 Q4W	81.5/181 (45.0)	75.2/180 (41.8)	1.18 (0.76, 1.82)	0.2295
M2302	AIN457 Q2W vs. Placebo	76.2/180 (42.3)	57.1/183 (31.2)	1.64 (1.05, 2.55)	0.0149**
	AIN457 Q4W vs. Placebo	83.1/180 (46.1)	57.1/183 (31.2)	1.90 (1.22, 2.96)	0.0022**
	AIN457 Q2W vs. AIN457 Q4W	76.2/180 (42.3)	83.1/180 (46.1)	0.86 (0.56, 1.32)	0.7537
Pooled data	AIN457 Q2W vs. Placebo	157.7/361 (43.7)	117.7/363 (32.4)	1.69 (1.24, 2.31)	0.0005
	AIN457 Q4W vs. Placebo	158.2/360 (43.9)	117.7/363 (32.4)	1.67 (1.22, 2.29)	0.0007
	AIN457 Q2W vs. AIN457 Q4W	157.7/361 (43.7)	158.2/360 (43.9)	1.01 (0.75, 1.37)	0.4706

- One-sided nominal p-values are presented.
- n* = rounded average number of subjects with response in 100 imputations.
- m = number of subjects evaluable.
- Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight. Study was also included as covariates in the pooled analysis.
- A comparison between secukinumab Q2W and Q4W dose regimens in each study and comparisons using pooled data are not part of the pre-defined testing hierarchy.

**Statistically significant based on the pre-defined testing hierarchy.
Source: [Study M2301-Table 14.2-1.1], [Study M2302-Table 14.2-1.1], [SCE Appendix 1-Table 3.1-1.1]

Figure 16 Forest plot of the treatment effect (95% CI) for HiSCR50 response at Week 16 (primary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)



- m=number of subjects evaluable.
- Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight and study.

Source: [SCE Appendix 1-Figure 3.1-1.1]

The results of the pre-defined sensitivity analyses (using the weighted average across screening and baseline visit assessments as baseline value) and a supplementary analysis (using a treatment policy strategy on all intercurrent events) on HiSCR50 response rate at Week 16 in each study are shown in **Table 18** Summary of HiSCR50 response analyses at Week 16 for study M2301- Full analysis set and **Table 19**. As a post-hoc sensitivity analysis, the primary analysis on HiSCR50 response rate at Week 16 was also repeated to include age, hsCRP and smoking status as additional covariates in the model, as the MAH considered these baseline factors associated with disease severity to be disproportionately distributed across the treatment groups. The results were consistent with the primary analysis results in both studies and in pooled data; notably, for study M2302, the odds ratio vs. placebo remained larger for the Q4W group compared to the Q2W group.

Table 18 Summary of HiSCR50 response analyses at Week 16 for study M2301- Full analysis set

Analysis	Response rate	Comparator	Odds ratio	95% CI
Primary analysis				
AIN457 Q2W (N=181)	45.0	Placebo	1.75	(1.12, 2.73)
AIN457 Q4W (N=180)	41.8	Placebo	1.48	(0.95, 2.32)
Placebo (N=180)	33.7			
Sensitivity analysis – using weighted average as baseline				
AIN457 Q2W (N=181)	41.9	Placebo	1.64	(1.05, 2.57)
AIN457 Q4W (N=180)	38.3	Placebo	1.38	(0.87, 2.17)
Placebo (N=180)	31.8			
Supplementary analysis – based on supplementary estimand				
AIN457 Q2W (N=181)	45.9	Placebo	1.82	(1.17, 2.84)
AIN457 Q4W (N=180)	41.2	Placebo	1.45	(0.93, 2.27)
Placebo (N=180)	33.6			
Post-hoc analysis 1 – adding age, CRP and smoking status as covariates				
AIN457 Q2W (N=181)	45.0	Placebo	1.84	(1.17, 2.91)
AIN457 Q4W (N=180)	41.8	Placebo	1.55	(0.98, 2.44)
Placebo (N=180)	33.7			
Post-hoc analysis 2 – using longitudinal mixed model				
AIN457 Q2W (N=166)	42.75	Placebo	1.82	(1.15, 2.86)
AIN457 Q4W (N=167)	36.87	Placebo	1.42	(0.90, 2.24)
Placebo (N=165)	29.11			

- Covariates for primary analysis, sensitivity and supplementary analysis included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight.
- For weighed average as baseline: Baseline is defined as the weighted average based on Screening visit 1 (with weight 1/6), Screening visit 2 (with weight 2/6), and the randomization visit (with weight 3/6).
- For post-hoc analysis 1: age, CRP and smoking status were added as additional covariates.
- For post-hoc analysis 2 (longitudinal mixed model): Covariates included in the model: treatment group, baseline AN count, Hurley stage, use of antibiotic, geographical region, baseline body weight, visit, and treatment group*visit; with unstructured covariance matrix.
- Source: Table 14.2-1.1, Table 14.2-1.7, Table 14.2-1.6, Table 14.2-26.1, Table 14.2-25.1

Source: M2301 CSR, Table 11-3

Table 19 Summary of HiSCR50 response analyses at Week 16 for study M2302- Full analysis set

Analysis	Response rate	Comparator	Odds ratio	95% CI
Primary analysis				
AIN457 Q2W (N=180)	42.3	Placebo	1.64	(1.05, 2.55)
AIN457 Q4W (N=180)	46.1	Placebo	1.90	(1.22, 2.96)
Placebo (N=183)	31.2			
Sensitivity Analysis – using weighted average as baseline				
AIN457 Q2W (N=180)	41.1	Placebo	1.77	(1.13, 2.79)
AIN457 Q4W (N=180)	44.4	Placebo	2.00	(1.28, 3.13)
Placebo (N=183)	28.7			
Supplementary Analysis – based on supplementary estimand				
AIN457 Q2W (N=180)	42.0	Placebo	1.57	(1.01, 2.44)
AIN457 Q4W (N=180)	46.1	Placebo	1.85	(1.19, 2.88)
Placebo (N=183)	31.7			
Post-hoc analysis 1 – adding age, CRP and smoking status as covariates				
AIN457 Q2W (N=180)	42.3	Placebo	1.64	(1.05, 2.57)
AIN457 Q4W (N=180)	46.1	Placebo	1.86	(1.20, 2.90)
Placebo (N=183)	31.2			
Post-hoc analysis 2 – using longitudinal mixed model				
AIN457 Q2W (N=180)	40.35	Placebo	1.56	(0.99, 2.46)
AIN457 Q4W (N=180)	43.36	Placebo	1.77	(1.13, 2.78)
Placebo (N=183)	30.19			

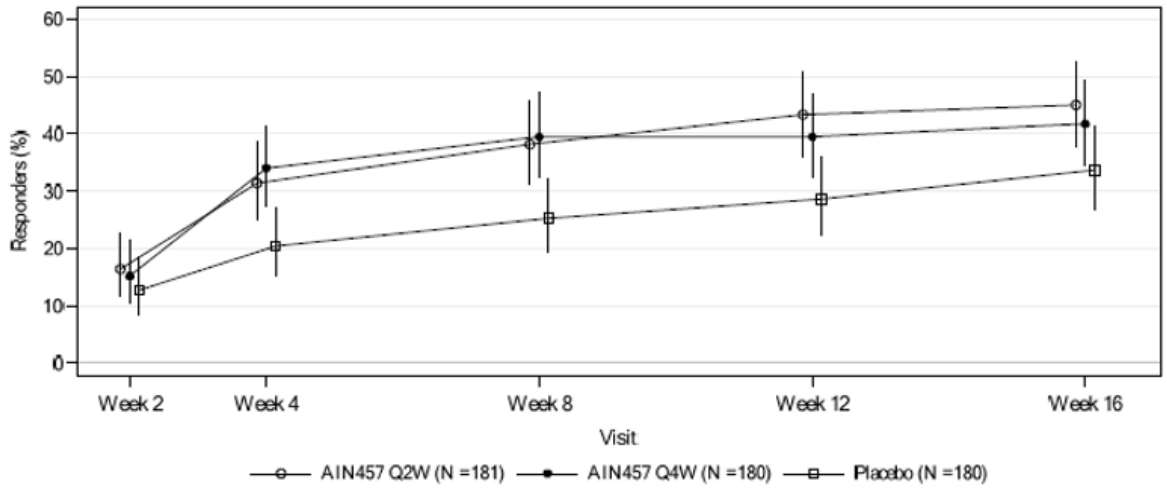
- Covariates for primary analysis, sensitivity and supplementary analysis included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight.
- For weighed average as baseline: Baseline is defined as the weighted average based on Screening visit 1 (with weight 1/6), Screening visit 2 (with weight 2/6), and the randomization visit (with weight 3/6).
- For post-hoc analysis 1: age, CRP and smoking status were added as additional covariates.
- For post-hoc analysis 2 (longitudinal mixed model): Covariates included in the model: treatment group, baseline AN count, Hurley stage, use of antibiotic, geographical region, baseline body weight, visit, and treatment group*visit; with unstructured covariance matrix.
- Source: Table 14.2-1.1, Table 14.2-1.7, Table 14.2-1.6, Table 14.2-26.1, Table 14.2-25.1.

Source: M2302 CSR, Table 11-3

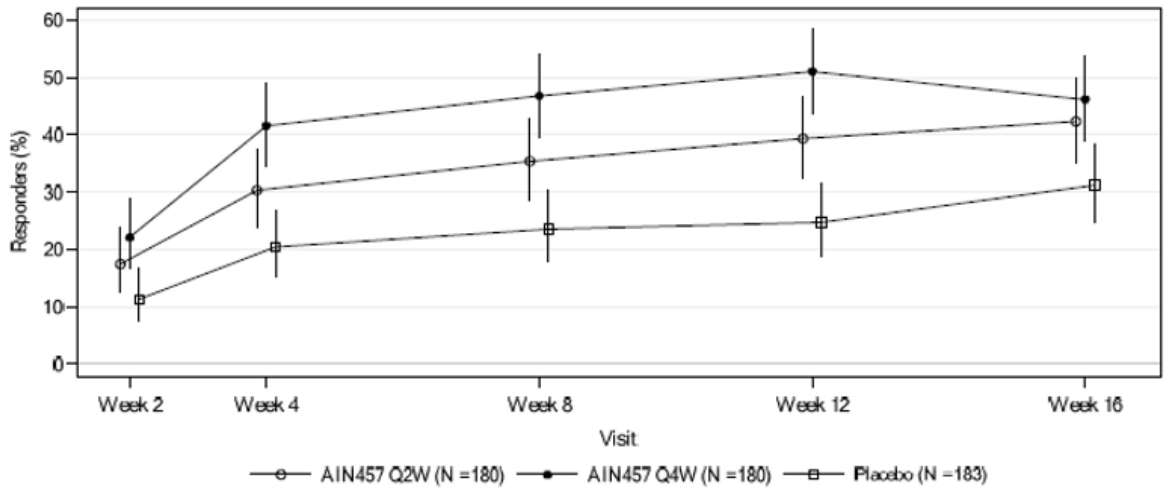
In both studies, a HiSCR50 response was observed as early as Week 2 for both secukinumab dose regimens, and the HiSCR50 response rate was higher in both secukinumab dose regimens than in placebo at all time points from Week 2 up to Week 16. The evolution of HiSCR50 response over time is displayed in **Figure 17**.

Figure 17 HiSCR50 responders up to Week 16 (mean response rate with 95% CI) (primary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)

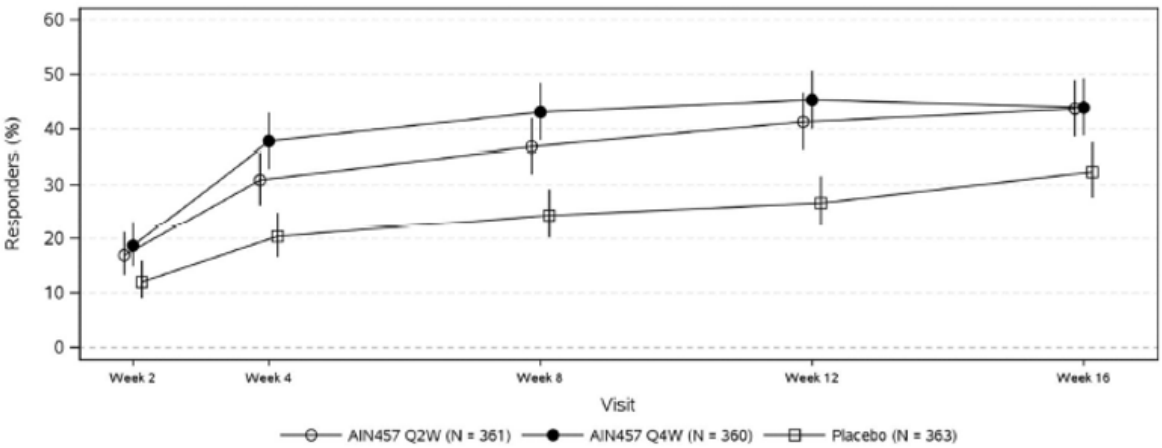
M2301



M2302



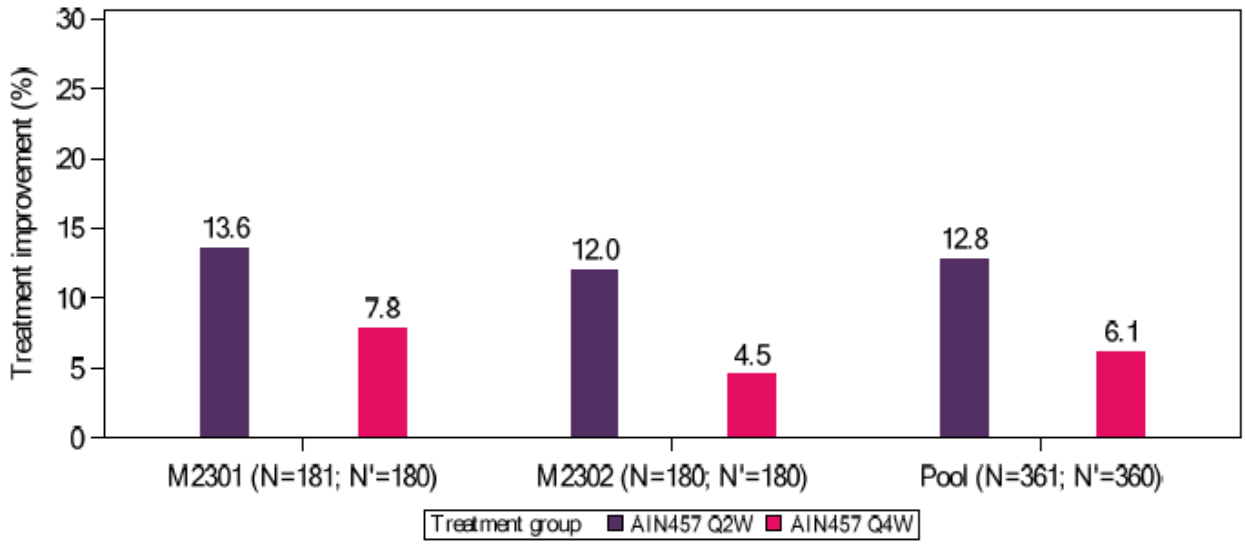
Pooled data



Source: [Study M2301-Figure 14.2-1.1], [Study M2302-Figure 14.2-1.1], [SCE Appendix 1-Figure 3.2-1.1]

Given the identical initial loading up to Week 4 in both secukinumab dose regimens, any differences observed up to Week 4 are likely due to chance or random imbalances as opposed to differences between the regimens. Thus, to better understand the effect of the maintenance regimens on response, the difference between Week 4 and Week 16 in the HiSCR50 response rates was calculated for each of the secukinumab dose regimens. The increase from Week 4 to Week 16 was greater for the secukinumab Q2W dose regimen compared to the secukinumab Q4W dose regimen in both studies and in pooled data (**Figure 18**). Odds ratios for Q2W vs. Q4W were also calculated using Week 4 HiSCR response status as a covariate; these are shown in **Table 20**.

Figure 18 HiSCR50 response improvement from Week 4 to Week 16 (primary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)



- Treatment improvement from Week 4 to Week 16 equals treatment response rate at Week 16 minus treatment response rate at Week 4.
- N=number of subjects in AIN457 Q2W dose regimen; N'=number of subjects in AIN457 Q4W dose regimen.
Source: [SCE Appendix 1-Figure 3.10-1.1]

Table 20 Logistic regression analysis of HiSCR response at Week 16 (primary estimand, sensitivity analysis: adjusting for differences at Week 4, observed data) Full analysis set (Table prepared by CHMP)

M2301

Treatment comparison "test" vs. "control"	"test" n/m (%)	"control" n/m (%)	Odds ratio estimate (95% CI)	One-sided p-value
AIN457 Q2W vs. AIN457 Q4W	79/166 (47.6)	70/167 (41.9)	1.44 (0.90, 2.32)	0.0653

M2302

Treatment comparison "test" vs. "control"	"test" n/m (%)	"control" n/m (%)	Odds ratio estimate (95% CI)	One-sided p-value
AIN457 Q2W vs. AIN457 Q4W	73/169 (43.2)	79/168 (47.0)	1.05 (0.65, 1.70)	0.4168

- n = number of subjects with observed response.
- m = number of subjects evaluable.
- Covariates included in the model: treatment group, geographical region, Hurley stage, baseline AN count, use of antibiotic, baseline body weight, and HiSCR response at Week 4.

Sources: M2301 CSR, Table 14.2-27.1; M2302 CSR, Table 14.2-27.1

Higher HiSCR responses

HiSCR75, HiSCR90 and HiSCR100 response rates at Week 16 are shown in **Table 21**, and **Figure 19** displays the evolution of treatment response over time in pooled data.

Table 21 Logistic regression analysis of HiSCR75, HiSCR90, HiSCR100 response at Week 16 (primary estimand, multiple imputation) (M2301 and M2302) (Full analysis set)

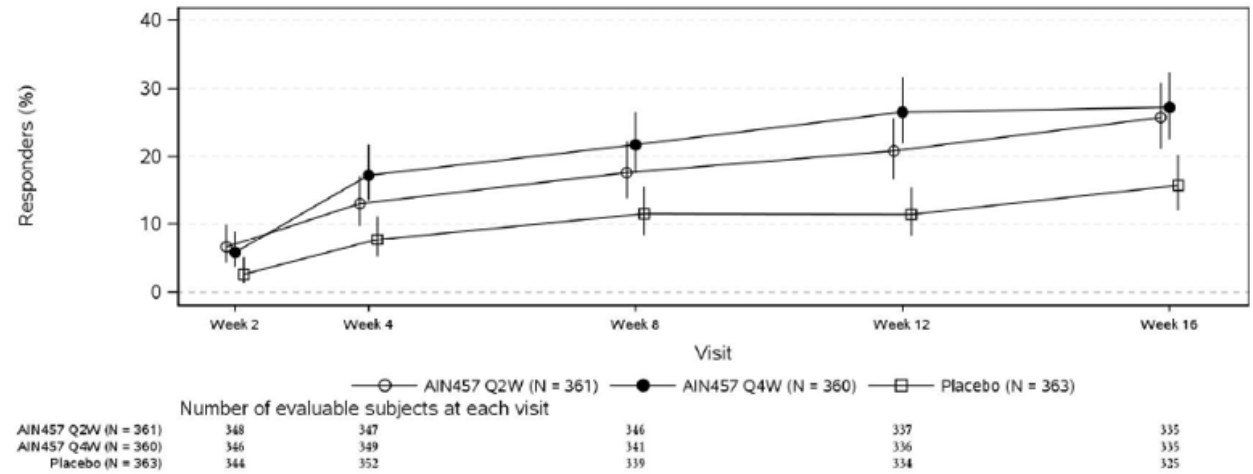
Response criterion	Treatment comparison "test" vs. "control"	_"test"_ n*/m (%)	_"control"_ n*/m (%)	Odds ratio estimate (95%CI)
M2301				
HiSCR75	AIN457 Q2W vs. Placebo	47.8/181 (26.4)	29.8/180 (16.5)	1.93 (1.13, 3.29)
	AIN457 Q4W vs. Placebo	40.7/180 (22.6)	29.8/180 (16.5)	1.54 (0.89, 2.65)
	AIN457 Q2W vs. AIN457 Q4W	47.8/181 (26.4)	40.7/180 (22.6)	1.26 (0.76, 2.06)
HiSCR90	AIN457 Q2W vs. Placebo	25.9/181 (14.3)	12.8/180 (7.1)	2.40 (1.15, 5.00)
	AIN457 Q4W vs. Placebo	24.4/180 (13.5)	12.8/180 (7.1)	2.18 (1.04, 4.57)
	AIN457 Q2W vs. AIN457 Q4W	25.9/181 (14.3)	24.4/180 (13.5)	1.10 (0.59, 2.04)
HiSCR100	AIN457 Q2W vs. Placebo	21.8/181 (12.0)	8.7/180 (4.8)	3.04 (1.28, 7.18)
	AIN457 Q4W vs. Placebo	18.8/180 (10.4)	8.7/180 (4.8)	2.57 (1.07, 6.19)
	AIN457 Q2W vs. AIN457 Q4W	21.8/181 (12.0)	18.8/180 (10.4)	1.18 (0.59, 2.35)
M2302				
HiSCR75	AIN457 Q2W vs. Placebo	41.7/180 (23.2)	24.8/183 (13.5)	1.98 (1.13, 3.46)
	AIN457 Q4W vs. Placebo	55.1/180 (30.6)	24.8/183 (13.5)	2.87 (1.67, 4.92)
	AIN457 Q2W vs. AIN457 Q4W	41.7/180 (23.2)	55.1/180 (30.6)	0.69 (0.43, 1.12)
HiSCR90	AIN457 Q2W vs. Placebo	20.8/180 (11.6)	10.7/183 (5.8)	2.13 (0.97, 4.69)
	AIN457 Q4W vs. Placebo	28.8/180 (16.0)	10.7/183 (5.8)	3.10 (1.46, 6.58)
	AIN457 Q2W vs. AIN457 Q4W	20.8/180 (11.6)	28.8/180 (16.0)	0.69 (0.37, 1.28)
HiSCR100	AIN457 Q2W vs. Placebo	13.6/180 (7.5)	8.4/183 (4.6)	1.77 (0.71, 4.44)
	AIN457 Q4W vs. Placebo	14.5/180 (8.1)	8.4/183 (4.6)	1.90 (0.77, 4.68)
	AIN457 Q2W vs. AIN457 Q4W	13.6/180 (7.5)	14.5/180 (8.1)	0.93 (0.42, 2.08)

- n* = rounded average number of subjects with response in 100 imputations
- m = number of subjects evaluable.
- Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight.

Source: [Study M2301-Table 14.2-11.1], [Study M2302-Table 14.2-11.1]

Figure 19 HiSCR75/90/100 responders up to Week 16 (mean response rate with 95% CI) (primary estimand, observed data) (pooled data) Full analysis set

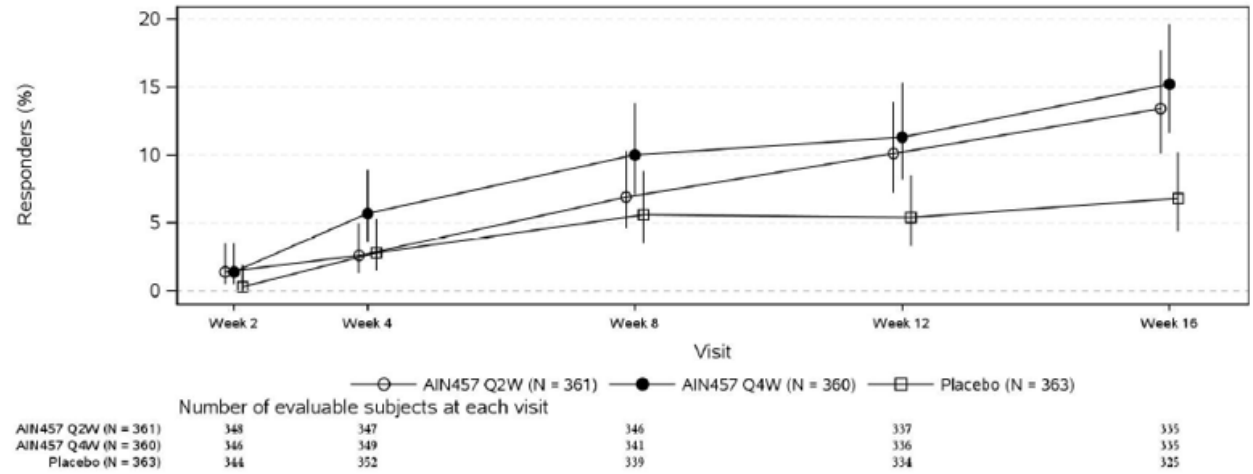
Parameter : HiSCR75



Number of evaluable subjects at each visit

AIN457 Q2W (N = 361)	348	347	346	337	335
AIN457 Q4W (N = 360)	346	349	341	336	335
Placebo (N = 363)	344	352	339	334	325

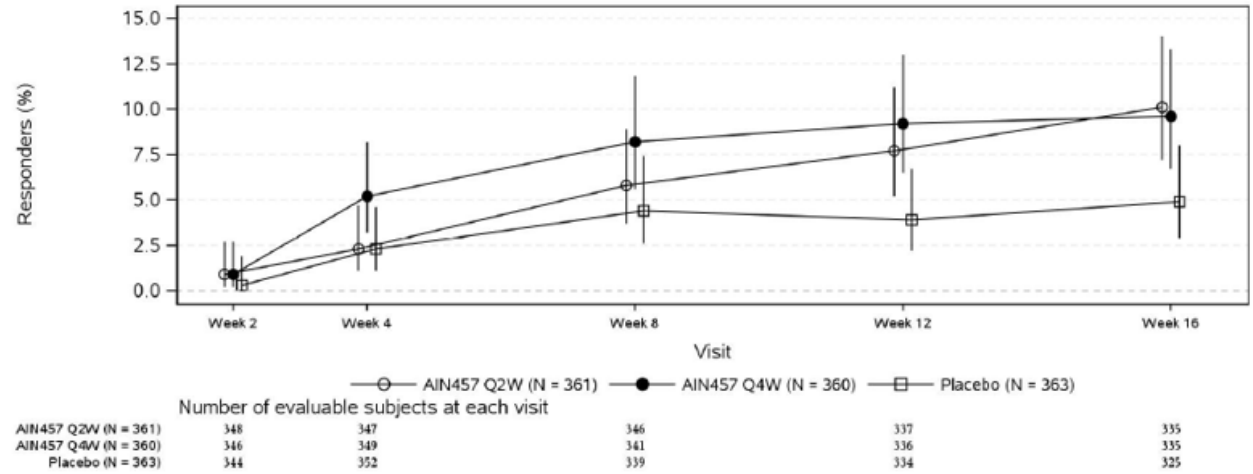
Parameter : HiSCR90



Number of evaluable subjects at each visit

AIN457 Q2W (N = 361)	348	347	346	337	335
AIN457 Q4W (N = 360)	346	349	341	336	335
Placebo (N = 363)	344	352	339	334	325

Parameter : HiSCR100



Number of evaluable subjects at each visit

AIN457 Q2W (N = 361)	348	347	346	337	335
AIN457 Q4W (N = 360)	346	349	341	336	335
Placebo (N = 363)	344	352	339	334	325

Source: SCE Appendix, Figure 3.4-1.1

Secondary endpoints – placebo-controlled period

AN count

In both studies, the mean percentage change from baseline in AN count at Week 16 was larger (greater decrease in AN count) in both secukinumab dose regimens than in placebo (−46.8% in secukinumab Q2W, −42.4% in secukinumab Q4W, −24.3% in placebo in M2301; −39.3% in secukinumab Q2W, −45.5% in secukinumab Q4W, −22.4% in placebo in M2302). The estimated LS mean difference between treatment groups (secukinumab vs. placebo) for percentage change from baseline in AN count at Week 16 was statistically significant for the secukinumab Q2W dose regimen in both studies and for the secukinumab Q4W dose regimen in M2302. The secukinumab Q4W dose regimen in M2301 did not achieve statistical significance based on the testing hierarchy. The results are summarised in **Table 22**.

Table 22 Analysis of covariance of percentage change from baseline in AN count at Week 16 (secondary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)

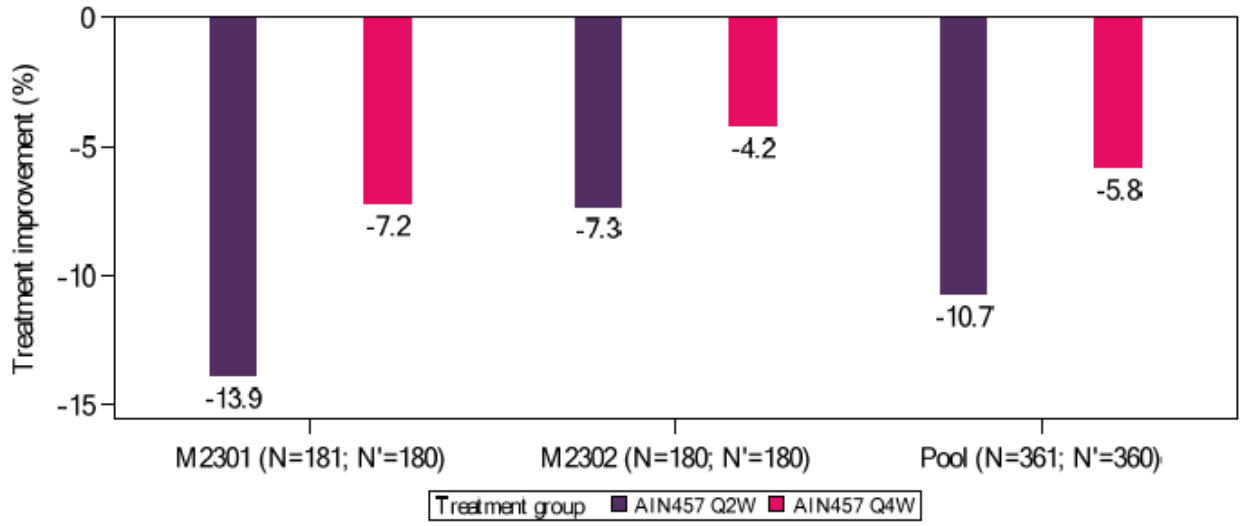
Study No.	Treatment comparison "test" vs. "control"	_"test"_ Mean (SE)	_"control"_ Mean (SE)	LS mean difference estimate (95%CI)	One-sided p-value
M2301	AIN457 Q2W vs. Placebo	-46.8 (3.33)	-24.3 (4.33)	-23.05 (-33.90, -12.21)	<0.0001**
	AIN457 Q4W vs. Placebo	-42.4 (4.01)	-24.3 (4.33)	-18.46 (-29.32, -7.60)	0.0004
	AIN457 Q2W vs. AIN457 Q4W	-46.8 (3.33)	-42.4 (4.01)	-4.59 (-15.37, 6.18)	0.2018
M2302	AIN457 Q2W vs. Placebo	-39.3 (4.43)	-22.4 (4.84)	-16.33 (-28.79, -3.88)	0.0051**
	AIN457 Q4W vs. Placebo	-45.5 (4.08)	-22.4 (4.84)	-22.94 (-35.24, -10.63)	0.0001**
	AIN457 Q2W vs. AIN457 Q4W	-39.3 (4.43)	-45.5 (4.08)	6.60 (-5.79, 19.00)	0.8517
Pooled data	AIN457 Q2W vs. Placebo	-43.1 (2.78)	-23.3 (3.25)	-19.98 (-28.27, -11.69)	<0.0001
	AIN457 Q4W vs. Placebo	-44.0 (2.85)	-23.3 (3.25)	-20.82 (-29.02, -12.62)	<0.0001
	AIN457 Q2W vs. AIN457 Q4W	-43.1 (2.78)	-44.0 (2.85)	0.84 (-7.39, 9.07)	0.5793

- One-sided nominal p-values are presented.
- The Mean is the pooled mean over 100 imputations. SE is the pooled standard error over 100 imputations.
- Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight. Study was also included as covariates in the pooled analysis.
- A comparison between secukinumab Q2W and Q4W dose regimens in each study and comparisons using pooled data are not part of the pre-defined testing hierarchy.

**Statistically significant based on the pre-defined testing hierarchy.
Source: [Study M2301-Table 14.2-2.1a], [Study M2302-Table 14.2-2.1a], [SCE Appendix 1-Table 3.1-1.2]

Given the identical initial loading up to Week 4 for both secukinumab dose regimens, the difference between Week 4 and Week 16 in the percentage change from baseline in AN count was calculated for each of the secukinumab dose regimens. The results are shown in **Figure 20**.

Figure 20 Treatment improvement of percentage change from baseline in AN count from Week 4 to Week 16 (secondary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)



- Treatment improvement from Week 4 to Week 16 equals percentage change from baseline at Week 16 minus percentage change from baseline at Week 4.
- N=number of subjects in AIN457 Q2W dose regimen; N'=number of subjects in AIN457 Q4W dose regimen.
Source: [SCE Appendix 1-Figure 3.10-1.2]

Flares

In both studies, the proportion of subjects experiencing flares over the 16 weeks of the placebo-controlled period was lower in both secukinumab dose regimens compared to placebo (15.4% in secukinumab Q2W, 23.2% in secukinumab Q4W, 29.0% in placebo in M2301; 20.1% in secukinumab Q2W, 15.6% in secukinumab Q4W, 27.0% in placebo in M2302). As seen in **Table 23**, the estimated odds ratio of secukinumab to placebo for the proportion of subjects experiencing flares over 16 weeks was statistically significant for the secukinumab Q2W dose regimen in M2301 and for the secukinumab Q4W dose regimen in M2302. Flare rate by visit is shown in **Figure 21** and change in flare rate from Week 4 to Week 16 is shown in **Figure 22**.

Table 23 Logistic regression analysis of flares over 16 weeks (secondary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)

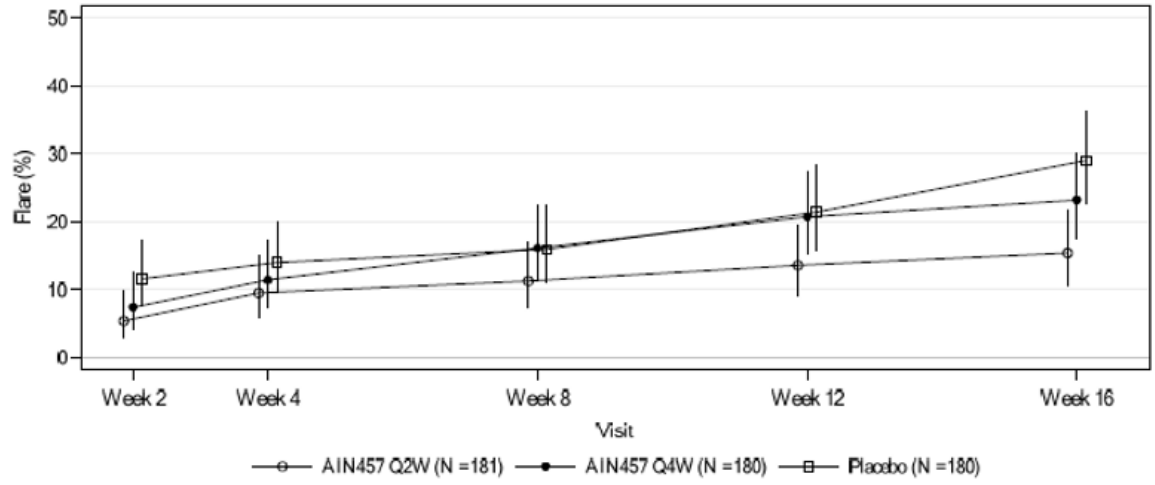
Study No.	Treatment comparison "test" vs. "control"	"test" n*/m (%)	"control" n*/m (%)	odds ratio estimate (95%CI)	One-sided p-value
M2301	AIN457 Q2W vs. Placebo	27.8/181 (15.4)	52.2/180 (29.0)	0.42 (0.25, 0.73)	0.0010**
	AIN457 Q4W vs. Placebo	41.7/180 (23.2)	52.2/180 (29.0)	0.71 (0.43, 1.17)	0.0926
	AIN457 Q2W vs. AIN457 Q4W	27.8/181 (15.4)	41.7/180 (23.2)	0.59 (0.34, 1.03)	0.0327
M2302	AIN457 Q2W vs. Placebo	36.1/180 (20.1)	49.5/183 (27.0)	0.68 (0.41, 1.14)	0.0732
	AIN457 Q4W vs. Placebo	28.0/180 (15.6)	49.5/183 (27.0)	0.49 (0.29, 0.84)	0.0049**
	AIN457 Q2W vs. AIN457 Q4W	36.1/180 (20.1)	28.0/180 (15.6)	1.39 (0.79, 2.44)	0.8748
Pooled data	AIN457 Q2W vs. Placebo	64.0/361 (17.7)	101.7/363 (28.0)	0.54 (0.37, 0.77)	0.0005
	AIN457 Q4W vs. Placebo	69.8/360 (19.4)	101.7/363 (28.0)	0.60 (0.42, 0.87)	0.0032
	AIN457 Q2W vs. AIN457 Q4W	64.0/361 (17.7)	69.8/360 (19.4)	0.89 (0.60, 1.31)	0.2712

- One-sided nominal p-values are presented.
- n*=rounded average number of subjects with response in 100 imputations.
- m=number of subjects evaluable.
- Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight. Study was also included as covariates in the pooled analysis.
- A comparison between secukinumab Q2W and Q4W dose regimens in each study and comparisons using pooled data are not part of the pre-defined testing hierarchy.

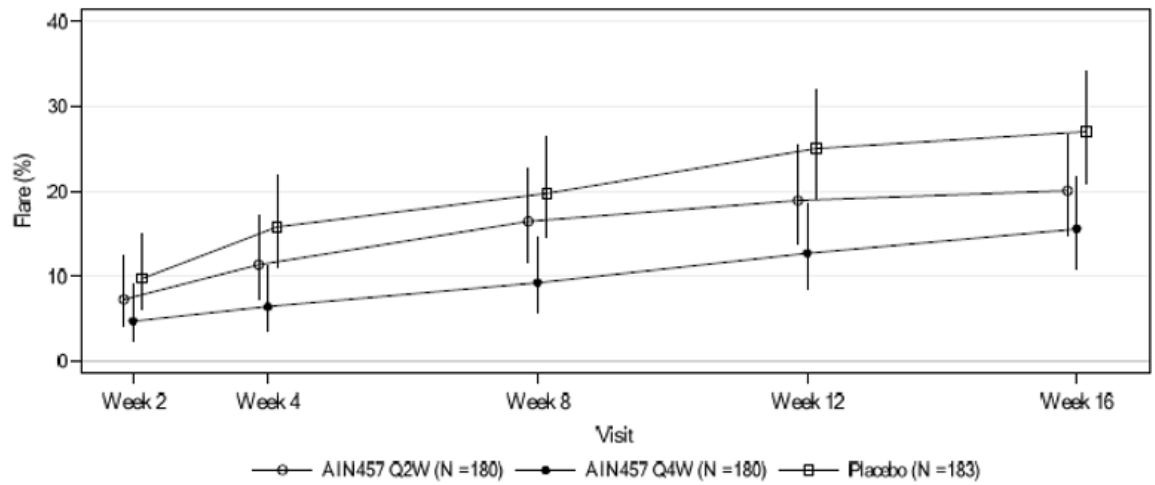
**Statistically significant based on the pre-defined testing hierarchy.
Source: [Study M2301-Table 14.2-3.1], [Study M2302-Table 14.2-3.1], [SCE Appendix 1-Table 3.1-1.3]

Figure 21 Flares over time up to Week 16 (mean response rate with 95% CI) (secondary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)

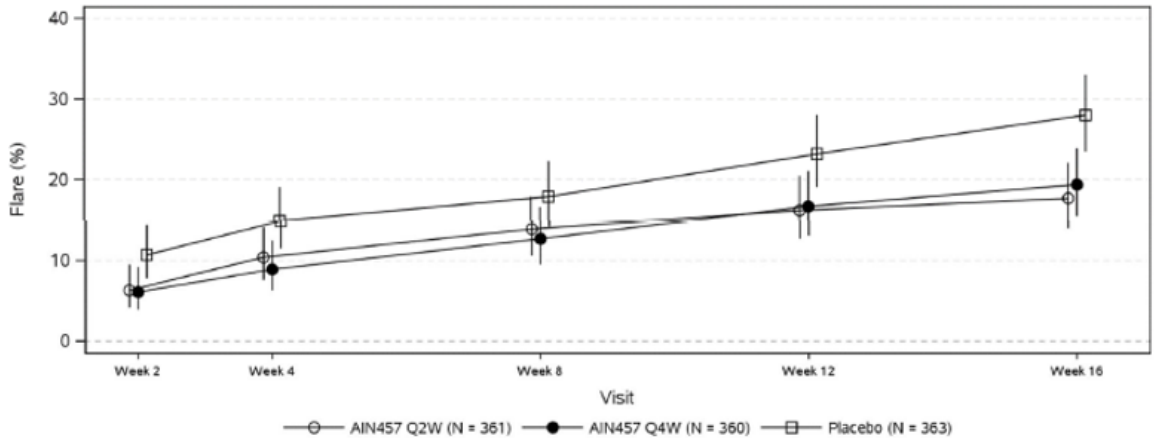
M2301



M2302

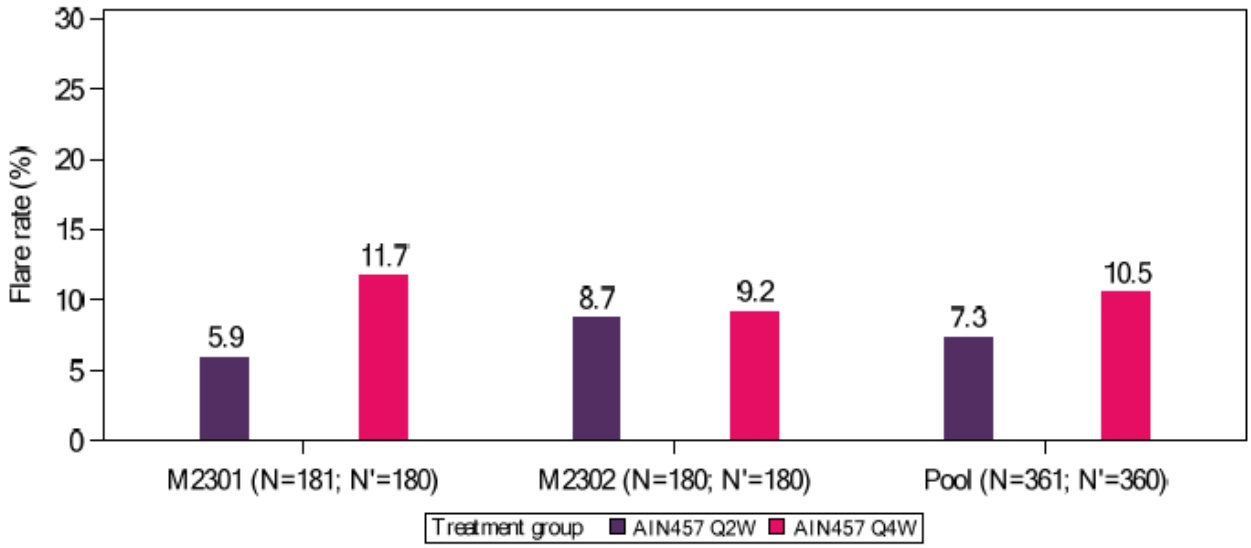


Pooled data



Source: [Study M2301-Figure 14.2-3.1], [Study M2302-Figure 14.2-3.1], [SCE Appendix 1-Figure 3.2-1.4]

Figure 22 Flares over time from Week 4 to Week 16 (secondary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)



- N=number of subjects in AIN457 Q2W dose regimen; N'=number of subjects in AIN457 Q4W dose regimen.
- The proportion of subjects experiencing flares up to Week 16 minus the proportion of subjects experiencing flares up to Week 4 is displayed.

Source: [SCE Appendix 1-Figure 3.10-1.3]

Pain – NRS30

As indicated above, pain response was primarily analysed among subjects with baseline NRS ≥3 (N=769, i.e., about 71% of the total number of subjects) and was only pre-planned to be analysed with pooled data. In the pooled analysis for skin pain, the NRS30 response rate at Week 16 was higher in both secukinumab dose regimens than in placebo (36.6% in secukinumab Q2W, 33.5% in secukinumab Q4W, 23.0% in placebo). The estimated odds ratio of secukinumab to placebo for NRS30 response rate at Week 16 was statistically significant for the secukinumab Q2W dose regimen; the odds ratio of the Q4W dose regimen to placebo was not statistically significant despite a numerically quite similar treatment difference. The results for the pooled data are summarised in **Table 24**, and the forest plot in **Figure 23** also displays NRS30 results from both individual studies.

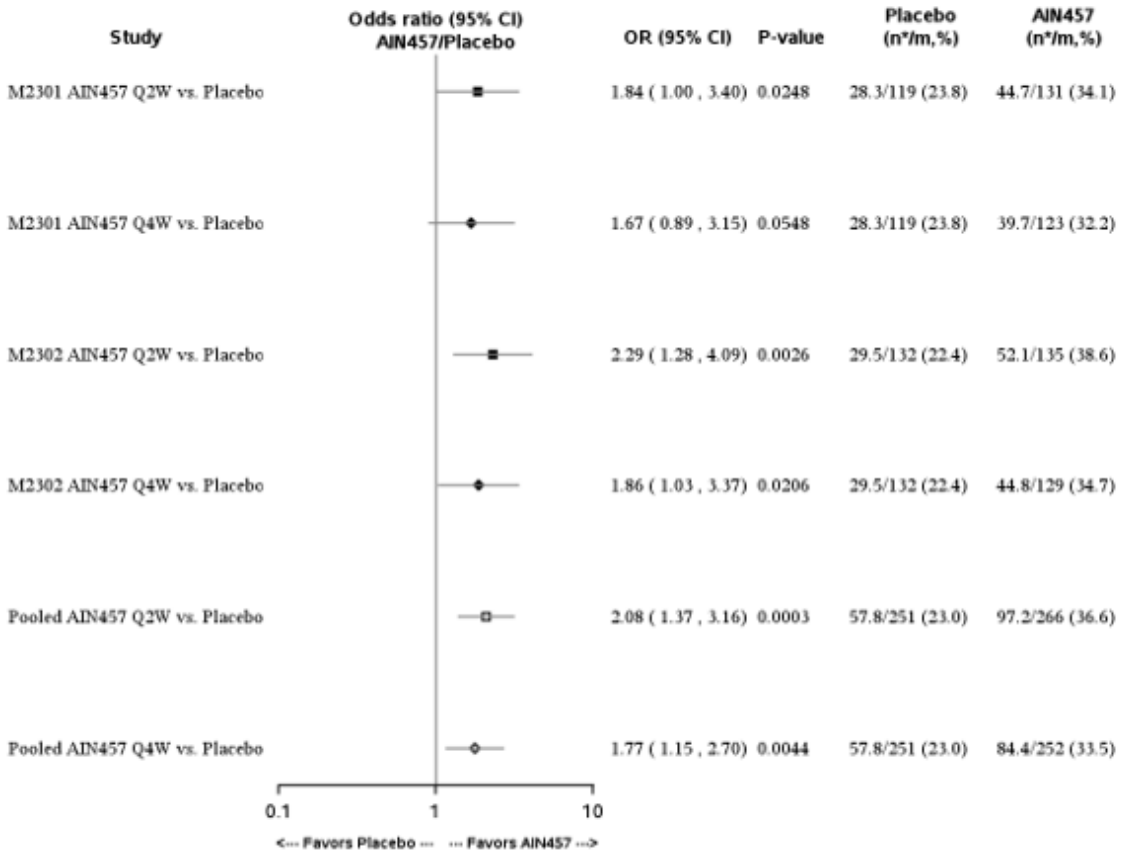
Table 24 Logistic regression analysis of NRS30 response at Week 16 (secondary estimand, multiple imputation) (pooled data) (Full analysis set)

Study No.	Treatment comparison "test" vs. "control"	"test" n*/m (%)	"control" n*/m (%)	odds ratio estimate (95%CI)	One-sided p-value
Pooled data	AIN457 Q2W vs. Placebo	97.2/266 (36.6)	57.8/251 (23.0)	2.08 (1.37, 3.16)	0.0003**
	AIN457 Q4W vs. Placebo	84.4/252 (33.5)	57.8/251 (23.0)	1.77 (1.15, 2.70)	0.0044
	AIN457 Q2W vs. AIN457 Q4W	97.2/266 (36.6)	84.4/252 (33.5%)	1.18 (0.80, 1.73)	0.2010

- One-sided nominal p-values are presented.
- n*=rounded average number of subjects with response in 100 imputations.
- m=number of subjects evaluable.
- Covariates included in the model: treatment group, Hurley stage, baseline NRS; strata variables: geographical region, use of antibiotic, baseline body weight, study.
- NRS is the numeric rating scale of the Patient's Global Assessment of Skin Pain – at worst (averaged over the last 7 days).
- Only subjects with a baseline NRS ≥ 3 are included.
- NRS30 is defined as at least 30% reduction and at least 2 unit reduction from baseline NRS.
- A comparison between secukinumab Q2W and Q4W dose regimens is not part of the pre-defined testing hierarchy.

**Statistically significant based on the pre-defined testing hierarchy.
Source: [Study M2301-Table 14.2-4.1 fix], [Study M2302-Table 14.2-4.1 fix]

Figure 23 Forest plot of the treatment effect (95% CI) for NRS30 response at Week 16 (secondary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)

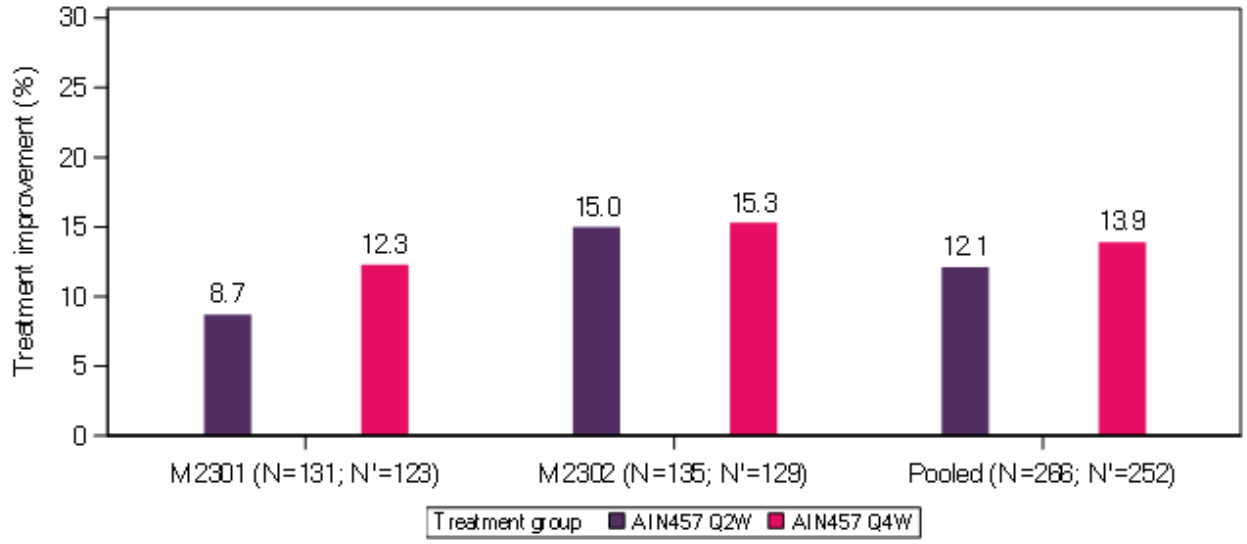


- m=number of subjects evaluable.
- Covariates included in the model: treatment group, Hurley stage, baseline NRS, geographical region, use of antibiotic, baseline body weight and study.
- NRS is the numeric rating scale of the Patient's Global Assessment of Skin Pain – at worst (averaged over the last 7 days).
- Only subjects with a baseline NRS ≥ 3 are included.
- NRS30 is defined as at least 30% reduction and at least 2 unit reduction from baseline NRS.
- Comparison vs. placebo in the study level is not part of the pre-defined testing hierarchy but rather the pooled analysis.

Source: [SCE Appendix 1-Figure 3.1-1.4 fix]

The difference between Week 4 and Week 16 in the NRS30 response rates is shown in **Figure 24**.

Figure 24 Treatment improvement of NRS30 response from Week 4 to Week 16 (secondary estimand, multiple imputation) (M2301, M2302 and pooled data) (Full analysis set)



- Treatment improvement from Week 4 to Week 16 equals treatment response rate at Week 16 minus treatment response rate at Week 4.
- N=number of subjects in AIN457 Q2W dose regimen; N'=number of subjects in AIN457 Q4W dose regimen.
Source: [SCE Appendix 1-Figure 3.10-1.4 fix]

The change from baseline in NRS score up to Week 16 was also analysed in all subjects in the FAS using MMRM model and pooled as-observed data (**Table 25**). The adjusted mean change from baseline in NRS score was larger in both secukinumab dose regimens than in placebo across all time points, with Week 16 values of −1.27 in the secukinumab Q2W, −1.10 in the secukinumab Q4W, and −0.54 in placebo. The estimated treatment difference (secukinumab – placebo) in change from baseline in NRS score at Week 16 (95% CI) was −0.74 (−1.06, −0.42) for the secukinumab Q2W dose regimen and −0.56 (−0.88, −0.23) for the secukinumab Q4W dose regimen.

Table 25 MMRM analysing change from baseline in Skin Pain/NRS score up to Week 16 (observed data) (pooled data) Full analysis set

		Within treatment		Treatment difference			
Visit	Treatment group	Adjusted mean	(SE)	Comparison	Effect estimate	(SE)	(95% CI)	Two-sided p-value
Week 2	AIN457 Q2W (n = 315)	-0.79	(0.09)	vs. Placebo	-0.58	(0.11)	(-0.79, -0.37)	<.0001
	AIN457 Q4W (n = 314)	-0.61	(0.09)	vs. Placebo	-0.39	(0.11)	(-0.60, -0.19)	0.0002
	Placebo (n = 311)	-0.21	(0.09)					
Week 4	AIN457 Q2W (n = 306)	-1.01	(0.10)	vs. Placebo	-0.55	(0.12)	(-0.79, -0.31)	<.0001
	AIN457 Q4W (n = 300)	-0.90	(0.10)	vs. Placebo	-0.44	(0.12)	(-0.68, -0.20)	0.0004
	Placebo (n = 307)	-0.46	(0.10)					
Week 8	AIN457 Q2W (n = 295)	-1.25	(0.11)	vs. Placebo	-0.81	(0.14)	(-1.09, -0.53)	<.0001
	AIN457 Q4W (n = 285)	-0.88	(0.11)	vs. Placebo	-0.44	(0.14)	(-0.72, -0.16)	0.0021
	Placebo (n = 290)	-0.43	(0.11)					
Week 12	AIN457 Q2W (n = 294)	-1.40	(0.12)	vs. Placebo	-0.95	(0.15)	(-1.25, -0.64)	<.0001
	AIN457 Q4W (n = 264)	-1.18	(0.12)	vs. Placebo	-0.72	(0.16)	(-1.03, -0.41)	<.0001
	Placebo (n = 282)	-0.46	(0.12)					
Week 16	AIN457 Q2W (n = 282)	-1.27	(0.12)	vs. Placebo	-0.74	(0.16)	(-1.06, -0.42)	<.0001
	AIN457 Q4W (n = 258)	-1.10	(0.13)	vs. Placebo	-0.56	(0.17)	(-0.88, -0.23)	0.0008
	Placebo (n = 263)	-0.54	(0.13)					

Covariates included in the model: treatment group, baseline Skin Pain/NRS score, Hurley stage, use of antibiotic, geographical region, baseline body weight, visit, study, and treatment group*visit; with unstructured covariance matrix.

Source: SCE Appendix 1 Addendum 1, Table 3.8-1.6 fix

Exploratory endpoints – placebo-controlled period

Inflammatory markers – hsCRP and ESR

The mean hsCRP from baseline to Week 2 to Week 16 (change from baseline to Week 16 in parentheses) was:

- M2301
    - Q2W: 16.93 mg/L to 11.79 mg/L to 11.82 (−5.11) mg/L
    - Q4W: 16.55 mg/L to 12.87 mg/L to 11.77 (−4.78) mg/L
    - Placebo: 13.16 mg/L to 16.07 mg/L to 15.27 (+2.11) mg/L
- M2302
    - Q2W: 20.39 mg/L to 14.65 mg/L to 13.84 (−6.55) mg/L
    - Q4W: 15.16 mg/L to 14.00 mg/L to 11.19 (−3.97) mg/L
    - Placebo: 15.65 mg/L to 16.02 mg/L to 14.11 (−1.54) mg/L
- Pooled data
    - Q2W: 18.65 mg/L to 13.21 mg/L to 12.84 (−5.81) mg/L
    - Q4W: 15.86 mg/L to 13.45 mg/L to 11.48 (−4.38) mg/L
    - Placebo: 14.42 mg/L to 16.04 mg/L to 14.69 (+0.27) mg/L.

The mean ESR from baseline to Week 2 to Week 16 (change from baseline to Week 16 in parentheses) was:

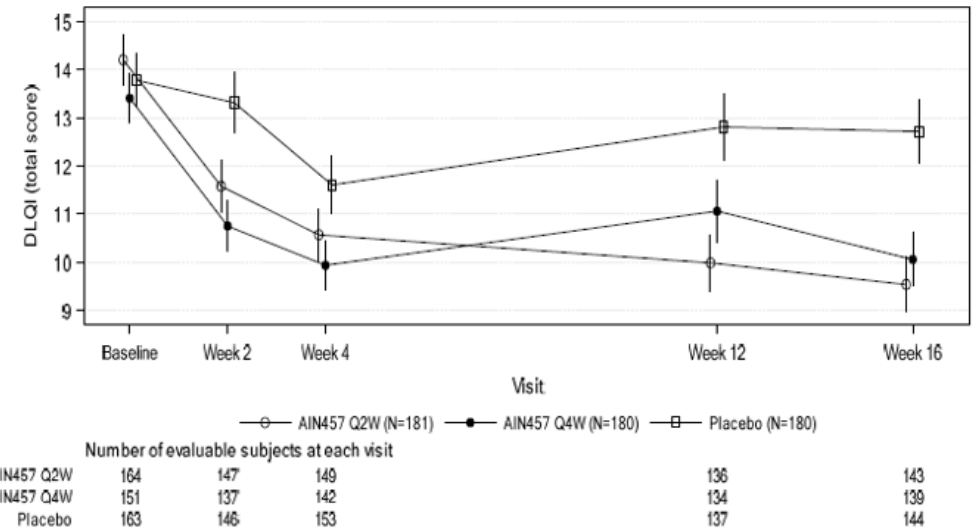
- M2301
    - Q2W: 38.1 mm/h to 34.4 mm/h to 33.7 (−4.4) mm/h
    - Q4W: 37.7 mm/h to 34.1 mm/h to 32.6 (−5.1) mm/h
    - Placebo: 34.4 mm/h to 33.4 mm/h to 34.2 (−0.2) mm/h
- M2302
    - Q2W: 37.5 mm/h to 32.7 mm/h to 32.7 (−4.8) mm/h
    - Q4W: 31.8 mm/h to 29.5 mm/h to 29.3 (−2.5) mm/h
    - Placebo: 35.8 mm/h to 32.5 mm/h to 32.4 (−3.4) mm/h
- Pooled data
    - Q2W: 37.8 mm/h to 33.6 mm/h to 33.2 (−4.6) mm/h
    - Q4W: 34.7 mm/h to 31.7 mm/h to 31.0 (−3.7) mm/h
    - Placebo: 35.1 mm/h to 33.0 mm/h to 33.3 (−1.8) mm/h.

Patient-reported outcomes – DLQI

In both studies, the mean DLQI total score decreased at Weeks 2 and 4 and then remained relatively stable up to Week 16 in both secukinumab dose regimens (**Figure 25**). The mean absolute change from baseline to Week 16 in the DLQI total score was −4.3 for Q2W, −3.5 for Q4W, and −1.2 for placebo in M2301; −4.3 for Q2W, −3.7 for Q4W, and −1.5 for placebo in M2302. DLQI response rates (defined as a decrease of ≥5.0 points from baseline and analysed among the subgroup with a baseline DLQI of ≥5.0) at Week 16 in the Q2W, Q4W and placebo groups, respectively, were 47.8%, 48.4% and 28.9% in M2301, and 37.5%, 47.2% and 31.7% in M2302.

Figure 25 DLQI (total score) up to Week 16 (mean +/- SE) (observed data) (M2301, M2302 and pooled data) (Full analysis set)

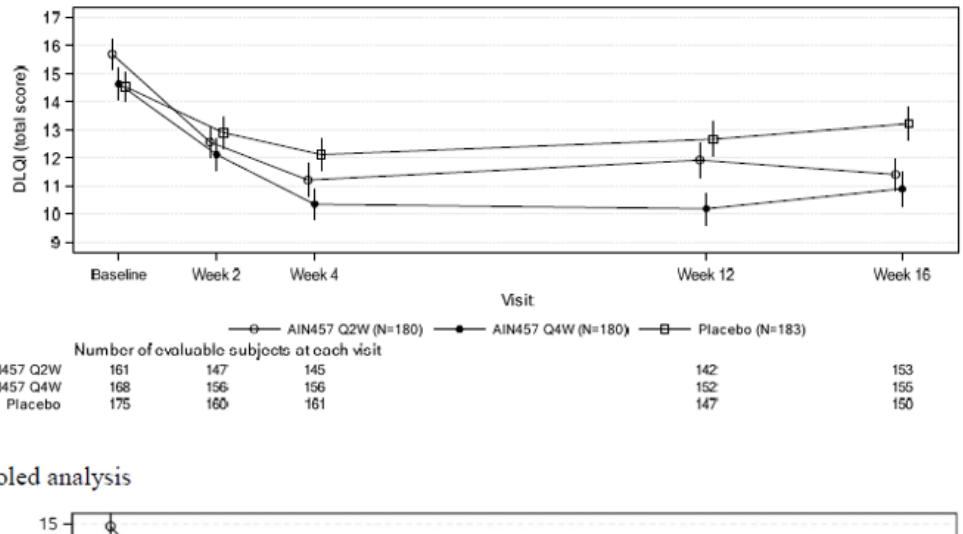
M2301



Number of evaluable subjects at each visit

AIN457 Q2W	164	147	149	136	143
AIN457 Q4W	151	137	142	134	139
Placebo	163	146	153	137	144

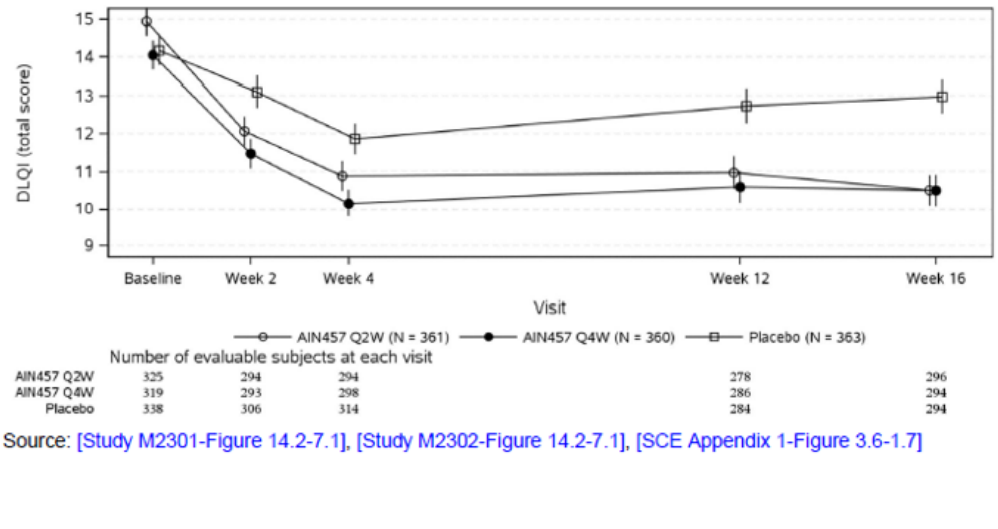
M2302



Number of evaluable subjects at each visit

AIN457 Q2W	161	147	145	142	153
AIN457 Q4W	168	156	156	152	155
Placebo	175	160	161	147	150

Pooled analysis



Number of evaluable subjects at each visit

AIN457 Q2W	325	294	294	278	296
AIN457 Q4W	319	293	298	286	294
Placebo	338	306	314	284	294

Source: [Study M2301-Figure 14.2-7.1], [Study M2302-Figure 14.2-7.1], [SCE Appendix 1-Figure 3.6-1.7]

Secondary endpoints – post Week 16

HiSCR response

Based on observed data, HiSCR50 response rate at Week 52 for the secukinumab Q2W and Q4W dose regimens was 56.4% and 56.3% in M2301, and 65.0% and 62.2% in M2302, respectively. Results based on a mixed effects logistic regression model (MELRM) for HiSCR50 up to Week 52 were in line with the results using observed data (M2301: 54.8% with Q2W and 55.3% with Q4W at Week 52; M2302: 63.4% with Q2W and 58.6% with Q4W at Week 52). In the groups switching from placebo to secukinumab at Week 16, HiSCR50 response rates increased from 30 – 37% at Week 16 to 48 – 55% at Week 52.

HiSCR50 response rates over time are shown in **Table 26** and **Figure 26**. A shift table for HiSCR response from Week 16 to Week 52 is displayed in **Table 27**.

Table 26 Number (%) of subjects with HiSCR50 response by visit up to Week 52 (observed data) (Full analysis set)

M2301

Visit	AIN457 Q2W – n/m (%)	AIN457 Q4W – n/m (%)	PBO-AIN457 Q2W – n/m (%)	PBO-AIN457 Q4W – n/m (%)
Week 16	78/163 (47.9%)	69/164 (42.1%)	27/81 (33.3%)	28/80 (35.0%)
Week 32	93/145 (64.1%)	83/148 (56.1%)	38/76 (50.0%)	37/74 (50.0%)
Week 52	66/117 (56.4%)	72/128 (56.3%)	28/ 58 (48.3%)	36/ 71 (50.7%)

Source: [Appendix 2 Study M2301 Table 14.2-1.4]

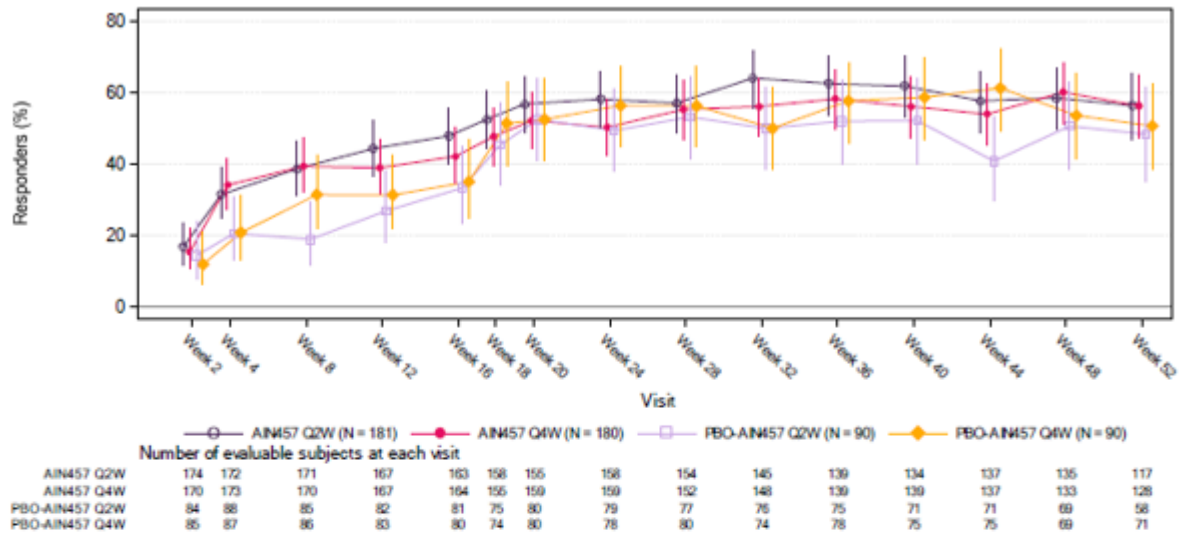
M2302

Visit	AIN457 Q2W – N/M (%)	AIN457 Q4W – N/M (%)	PBO-AIN457 Q2W – N/M (%)	PBO-AIN457 Q4W – N/M (%)
Week 16	71/167 (42.5%)	79/166 (47.6%)	29/78 (37.2%)	24/79 (30.4%)
Week 32	91/153 (59.5%)	90/149 (60.4%)	39/71 (54.9%)	41/72 (56.9%)
Week 52	89/137 (65.0%)	79/127 (62.2%)	35/64 (54.7%)	36/65 (55.4%)

Source: [Appendix 2 Study M2302 Table 14.2-1.4]

Figure 26 HiSCR50 responders up to Week 52 (mean response rate with 95% CI) (observed data) (Full analysis set)

M2301

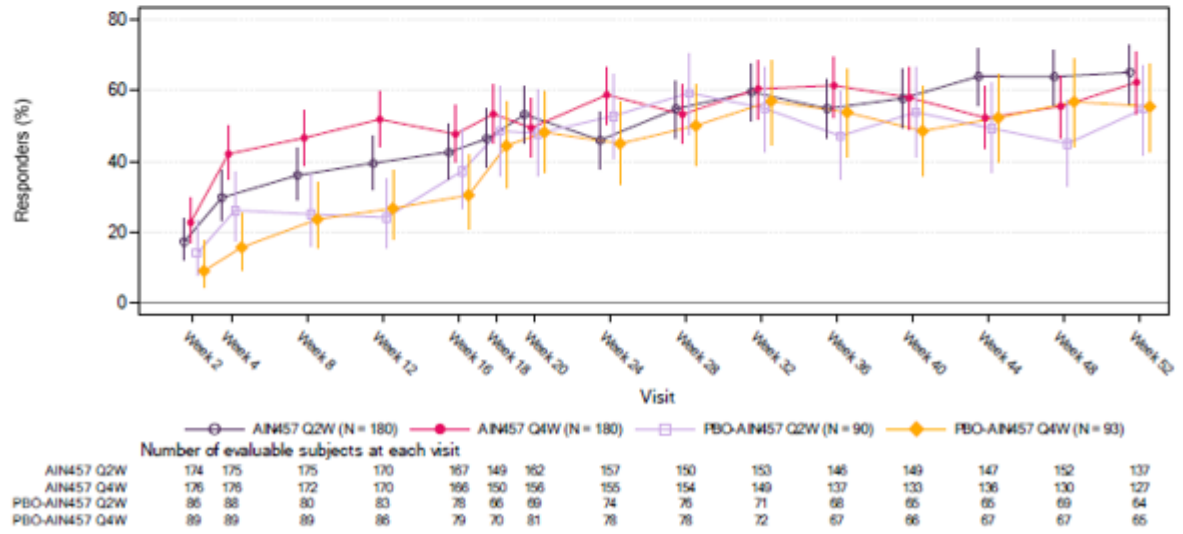


Number of evaluable subjects at each visit

AIN457 Q2W	174	172	171	167	163	158	155	158	154	145	139	134	137	135	117
AIN457 Q4W	170	173	170	167	164	155	159	159	152	148	139	139	137	133	128
PBO-AIN457 Q2W	84	88	85	82	81	75	80	79	77	76	75	71	71	69	58
PBO-AIN457 Q4W	85	87	86	83	80	74	80	78	80	74	78	75	75	69	71

Source: [Appendix 2 Study M2301 Figure 14.2-1.2, Table 14.2-1.4]

M2302



Number of evaluable subjects at each visit

AIN457 Q2W	174	175	175	170	167	149	162	157	150	153	146	149	147	152	137
AIN457 Q4W	176	176	172	170	166	150	156	155	154	149	137	133	136	130	127
PBO-AIN457 Q2W	86	88	80	83	78	66	69	74	76	71	68	65	65	69	64
PBO-AIN457 Q4W	89	89	89	86	79	70	81	78	78	72	67	66	67	67	65

Source: [Appendix 2 Study M2302 Figure 14.2-1.2, Table 14.2-1.4]

Table 27 Shift table for HiSCR response from Week 16 to Week 52 using observed pooled data (Full analysis set)

Treatment		Week 16	Week 52	
			Response	No Response
		n (%)	n (%)	n (%)
AIN457 Q2W (N=361)	Response	119 (48.0)	95 (79.8)	24 (20.2)
	No response	129 (52.0)	57 (44.2)	72 (55.8)
	Total	248 (100.0)	152 (61.3)	96 (38.7)
AIN457 Q4W (N=360)	Response	117 (47.0)	92 (78.6)	25 (21.4)
	No response	132 (53.0)	56 (42.4)	76 (57.6)
	Total	249 (100.0)	148 (59.4)	101 (40.6)
PBO-AIN457 Q2W (N=180)	Response	38 (32.5)	25 (65.8)	13 (34.2)
	No response	79 (67.5)	35 (44.3)	44 (55.7)
	Total	117 (100.0)	60 (51.3)	57 (48.7)
PBO-AIN457 Q4W (N=183)	Response	42 (33.3)	29 (69.0)	13 (31.0)
	No response	84 (66.7)	39 (46.4)	45 (53.6)
	Total	126 (100.0)	68 (54.0)	58 (46.0)

A subject must have both Week 16 and Week 52 values to be included.
Percentages for Week 16 are based on the total number of subjects and percentages for Week 52 are based on the number of subjects at Week 16 in the corresponding category.

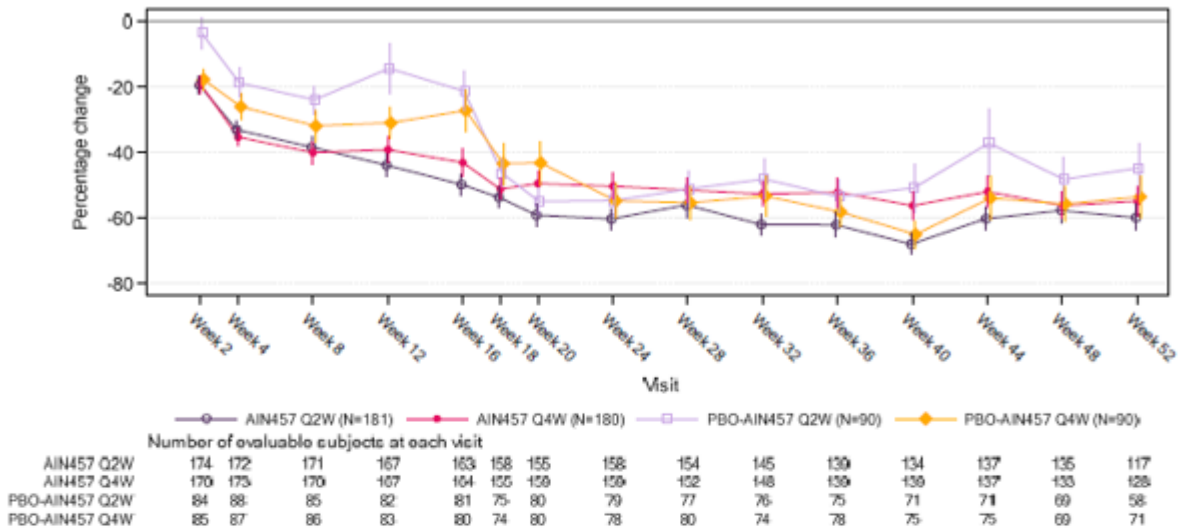
AN count

Based on observed data, the mean percentage change in AN count from baseline to Week 52 with the secukinumab Q2W and Q4W dose regimens was −59.9% and −54.9% in M2301, and −56.3% and −61.1% in M2302, respectively. The improvements in AN count based on a mixed model for repeated measures (MMRM) analysis up to Week 52 were in line with the results using observed data (M2301: -57.3% with Q2W and –53.0% with Q4W at Week 52; M2302: -53.4% with Q2W and –55.4% with Q4W at Week 52). In both studies, further decreases in AN counts from Week 16 to Week 52 were also observed in treatment groups switching from placebo to secukinumab at Week 16.

Percentage change over time in AN count is shown in **Figure 27**.

Figure 27 Percentage change from baseline in AN count up to Week 52 (mean +/- SE) (observed data) Full analysis set

M2301

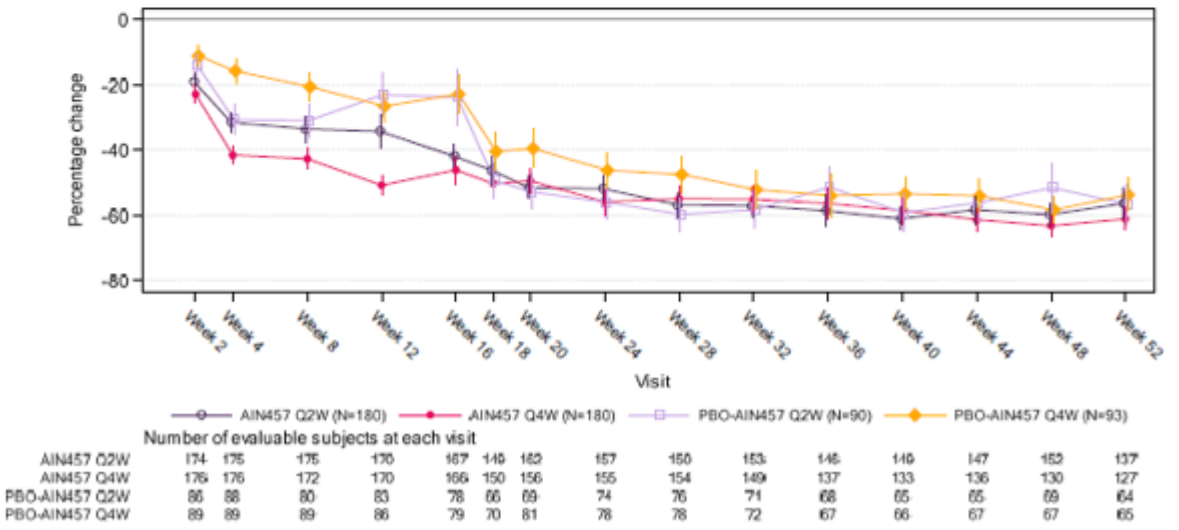


Number of evaluable subjects at each visit

AIN457 Q2W	174	172	171	167	163	158	155	158	154	145	139	134	137	135	117
AIN457 Q4W	170	175	170	167	164	155	159	159	152	148	139	139	137	133	128
PBO-AIN457 Q2W	84	88	85	82	81	75	80	79	77	76	75	71	71	69	58
PBO-AIN457 Q4W	85	87	86	83	80	74	80	78	80	74	78	75	75	69	71

Source: [Appendix 2 Study M2301 Figure 14.2-2.2a, Table 14.2-2.4a]

M2302



Number of evaluable subjects at each visit

AIN457 Q2W	174	175	175	170	167	149	162	157	150	153	146	149	147	152	137
AIN457 Q4W	176	176	172	170	166	150	156	155	154	149	137	133	136	130	127
PBO-AIN457 Q2W	86	88	80	83	78	66	69	74	76	71	68	65	65	69	64
PBO-AIN457 Q4W	89	89	89	86	79	70	81	78	78	72	67	66	67	67	65

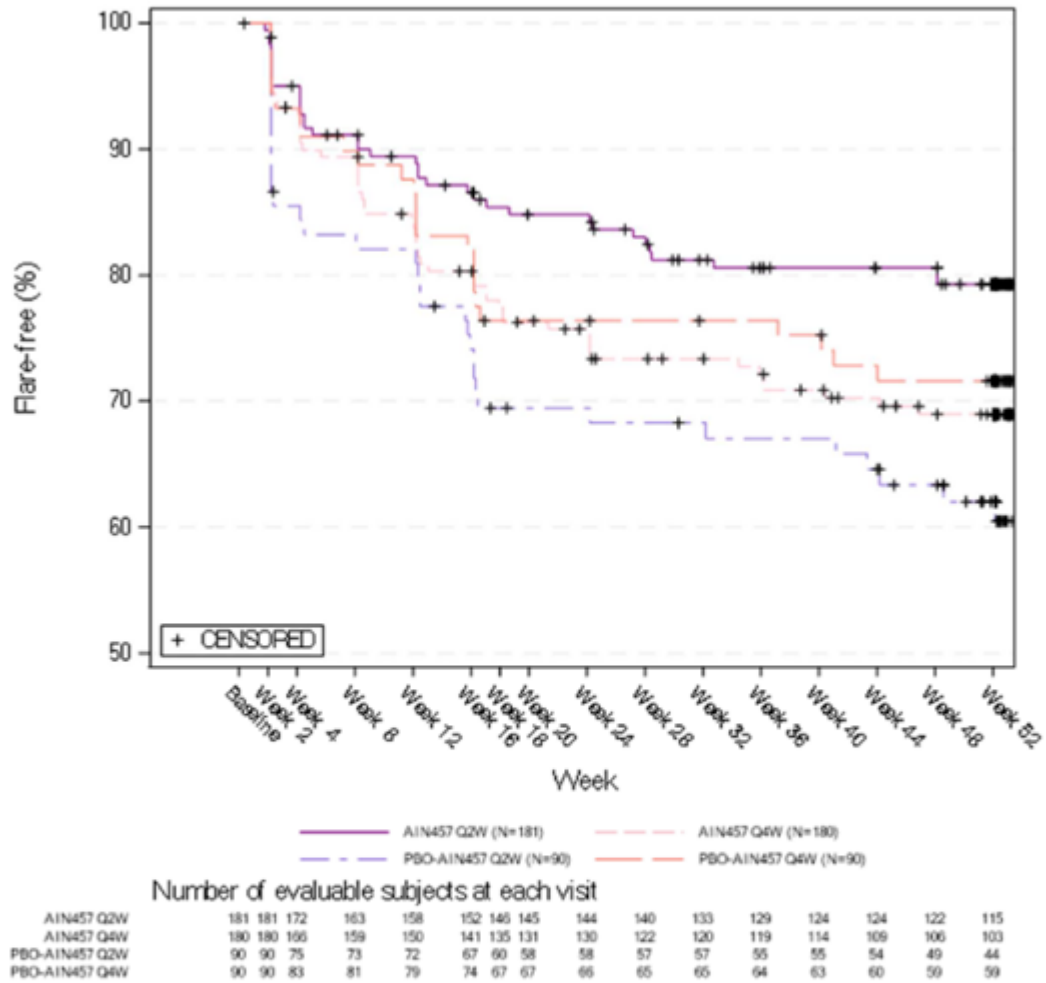
Source: [Appendix 2 Study M2302 Figure 14.2-2.2a, Table 14.2-2.4a]

Flares

The proportion of subjects experiencing flares over 52 weeks in the secukinumab Q2W and Q4W dose regimens was 18.1% and 30.1% in M2301, and 22.5% and 24.4% in M2302, respectively. **Figure 28** displays Kaplan-Meier estimates of time to disease flare up to Week 52 in both studies.

Figure 28 Kaplan Meier estimates of the time to disease flare up to Wk52 (observed data) (Full analysis set)

M2301



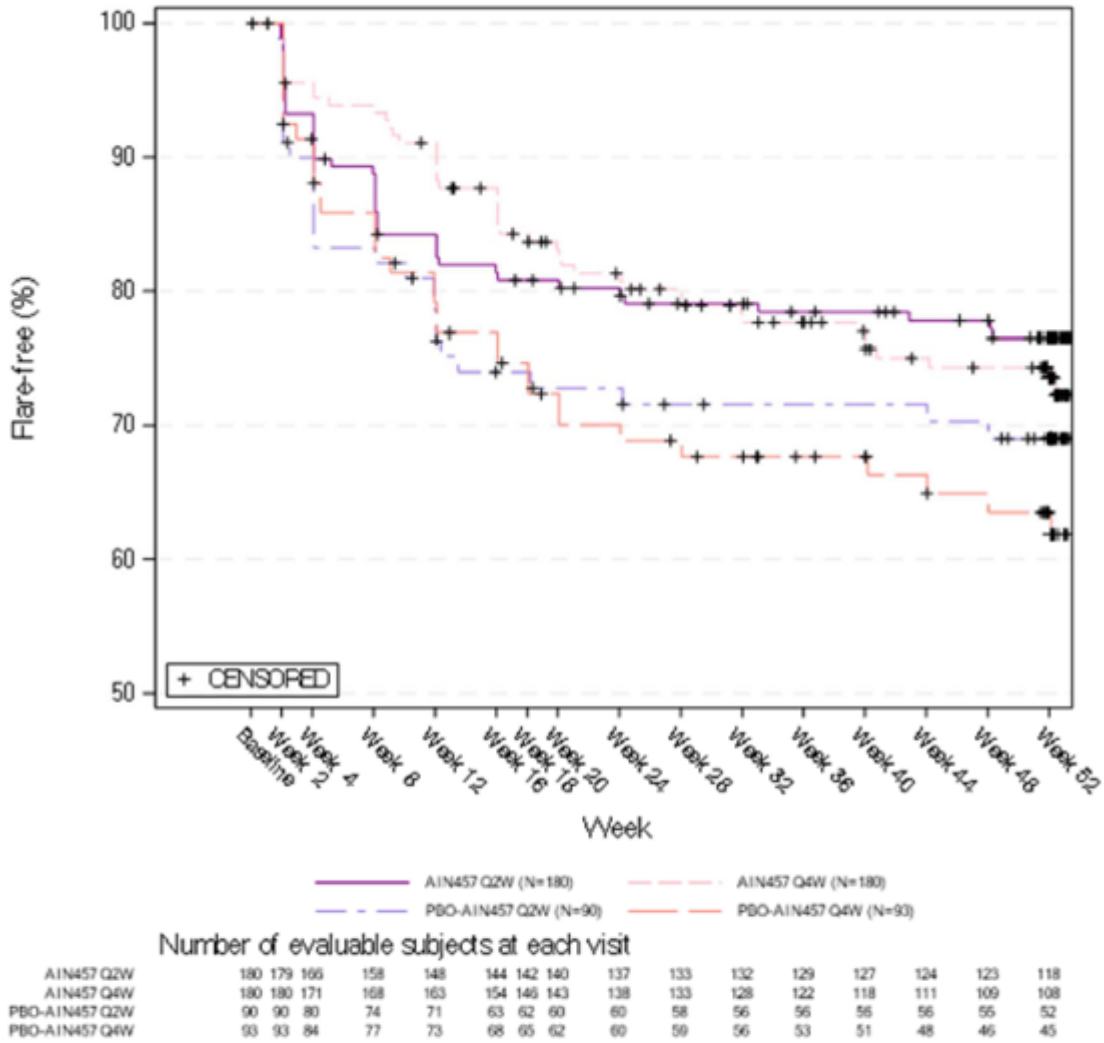
Number of evaluable subjects at each visit

AIN457 Q2W	181	181	172	163	158	152	146	145	144	140	133	129	124	124	122	115
AIN457 Q4W	180	180	166	159	150	141	135	131	130	122	120	119	114	109	106	103
PBO-AIN457 Q2W	90	90	75	73	72	67	60	58	58	57	57	55	55	54	49	44
PBO-AIN457 Q4W	90	90	83	81	79	74	67	67	66	65	65	64	63	60	59	59

-Observed data is used to fit the analysis model.
- Day 1 = date of randomization. Disease flare was derived relative to the end of Treatment Period 2 (Week 52 visit).
- Subjects who did not experience a flare, were censored at the date of their last non-missing visit.
- Subjects at risk = subjects who did not have flare and were not censored before or at the start of the specified day.
Source: [Appendix 2 Study M2301 Table 14.2-3.4.2]

Figure 28, cont'd Kaplan Meier estimates of the time to disease flare up to Wk52 (observed data) (Full analysis set)

M2302



Number of evaluable subjects at each visit

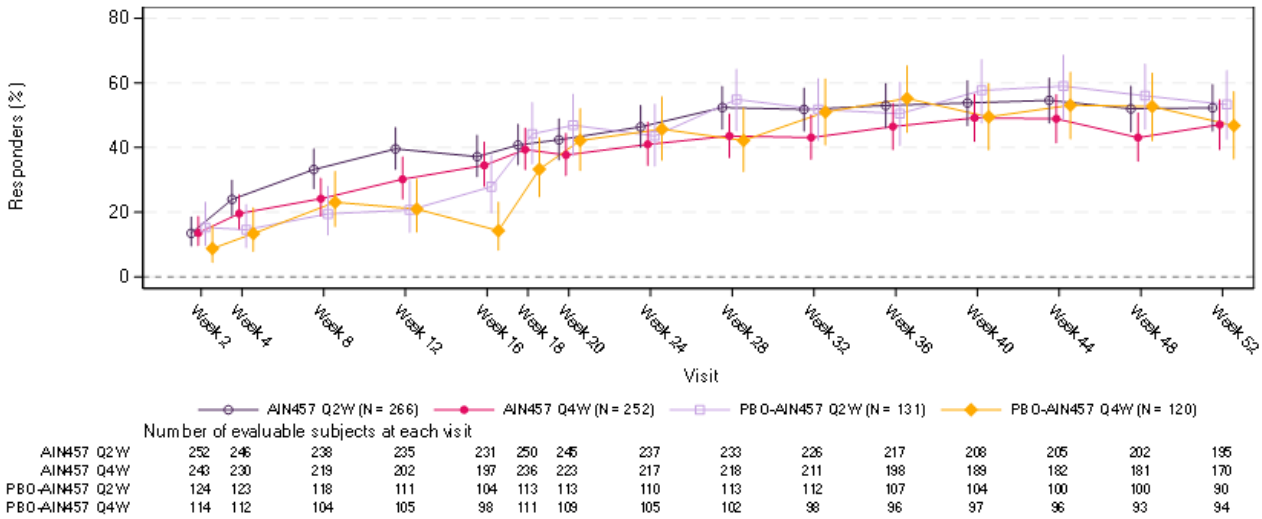
AIN457 Q2W	180	179	166	158	148	144	142	140	137	133	132	129	127	124	123	118
AIN457 Q4W	180	180	171	168	163	154	146	143	138	133	128	122	118	111	109	108
PBO-AIN457 Q2W	90	90	80	74	71	63	62	60	60	58	56	56	55	56	55	52
PBO-AIN457 Q4W	93	93	84	77	73	68	65	62	60	59	56	53	51	48	46	45

-Observed data is used to fit the analysis model.
- Day 1 = date of randomization. Disease flare was derived relative to the end of Treatment Period 2 (Week 52 visit).
- Subjects who did not experience a flare, were censored at the date of their last non-missing flare visit.
- Subjects at risk = subjects who did not have flare and were not censored before or at the start of the specified day.
Source: [Appendix 2 Study M2302 Table 14.2-3.4.2]

Pain - NRS30

NRS30 response by visit up to Week 52 was reported for subjects with a baseline NRS score ≥3. In the pooled data, the NRS30 response rate gradually increased through to Week 52 for both secukinumab dose regimens. Using observed data, NRS30 response rates at Week 52 were 52.3% and 47.1% for Q2W and Q4W, respectively. Response rates based on the MELRM at Week 52 were in line with the results using observed data (49.6% with Q2W and 44.2% with Q4W). Further increases in NRS30 response rates from Week 16 to Week 52 were also seen in the groups switching from placebo to secukinumab at Week 16. Evolution of response over time is displayed in **Figure 29**.

Figure 29 NRS30 responders up to Week 52 (mean response rate with 95% CI) (observed data) (pooled data) (Full analysis set)



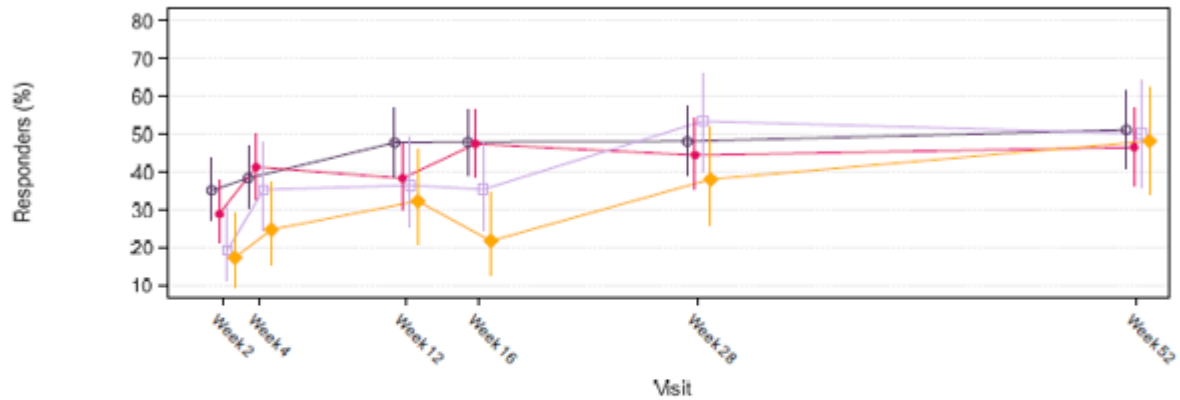
- NRS is the numeric rating scale of Patient`s Global Assessment of Skin Pain – at worst.
- Only subjects with a baseline NRS >= 3 are included.
- NRS30 is defined as at least 30% reduction and last least 2 unit reduction from baseline NRS.
- Pooled observed data is used
- Source: [Appendix 2 Figure 14.2-4.2 fix, Table 14.2-4.4 fix]

DLQI

At Week 52, DLQI response rates (decrease ≥ 5.0 points from baseline) for the Q2W and Q4W regimens, respectively, were 51.0% vs. 46.4% in study M2301, and 55.2% vs. 47.5% in study M2302. DLQI response rates over time are shown in **Figure 30**.

Figure 30 DLQI response rates up to Week 52 (mean response rate with 95% CI) (observed data) (Full analysis set)

M2301



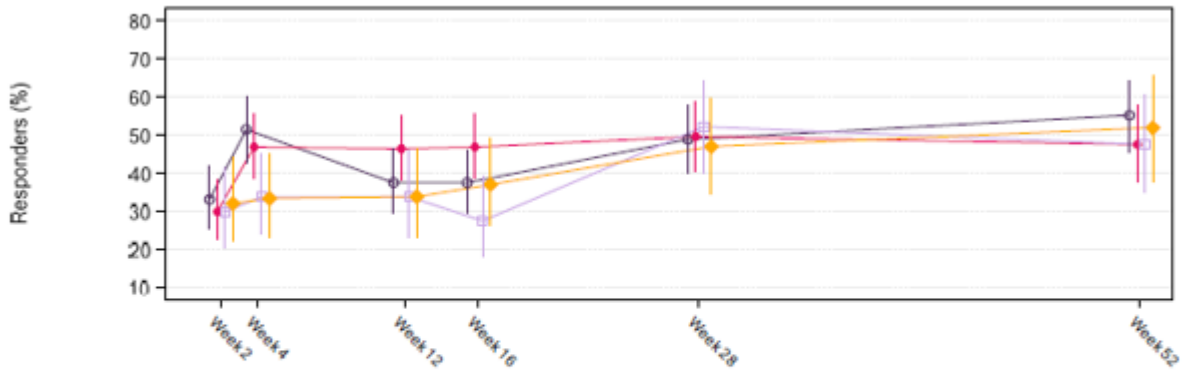
Number of evaluable subjects at each visit

AIN457 Q2W	137	141	126	136	123	66
AIN457 Q4W	125	131	123	131	115	97
PBO - AIN457 Q2W	68	71	66	68	60	50
PBO - AIN457 Q4W	64	65	56	60	58	52

- Only subjects with a baseline DLQI >= 5 are included.

Source: [Appendix 2 Study M2301 Table 14.2-9.6, Figure 14.2-7.4]

M2302



Number of evaluable subjects at each visit

AIN457 Q2W	139	136	136	144	131	116
AIN457 Q4W	144	143	140	143	125	101
PBO - AIN457 Q2W	77	80	71	73	69	61
PBO - AIN457 Q4W	75	75	68	73	66	52

- Only subjects with a baseline DLQI >= 5 are included.

Source: [Appendix 2 Study M2302 Table 14.2-9.6, Figure 14.2-7.4]

Ancillary analyses

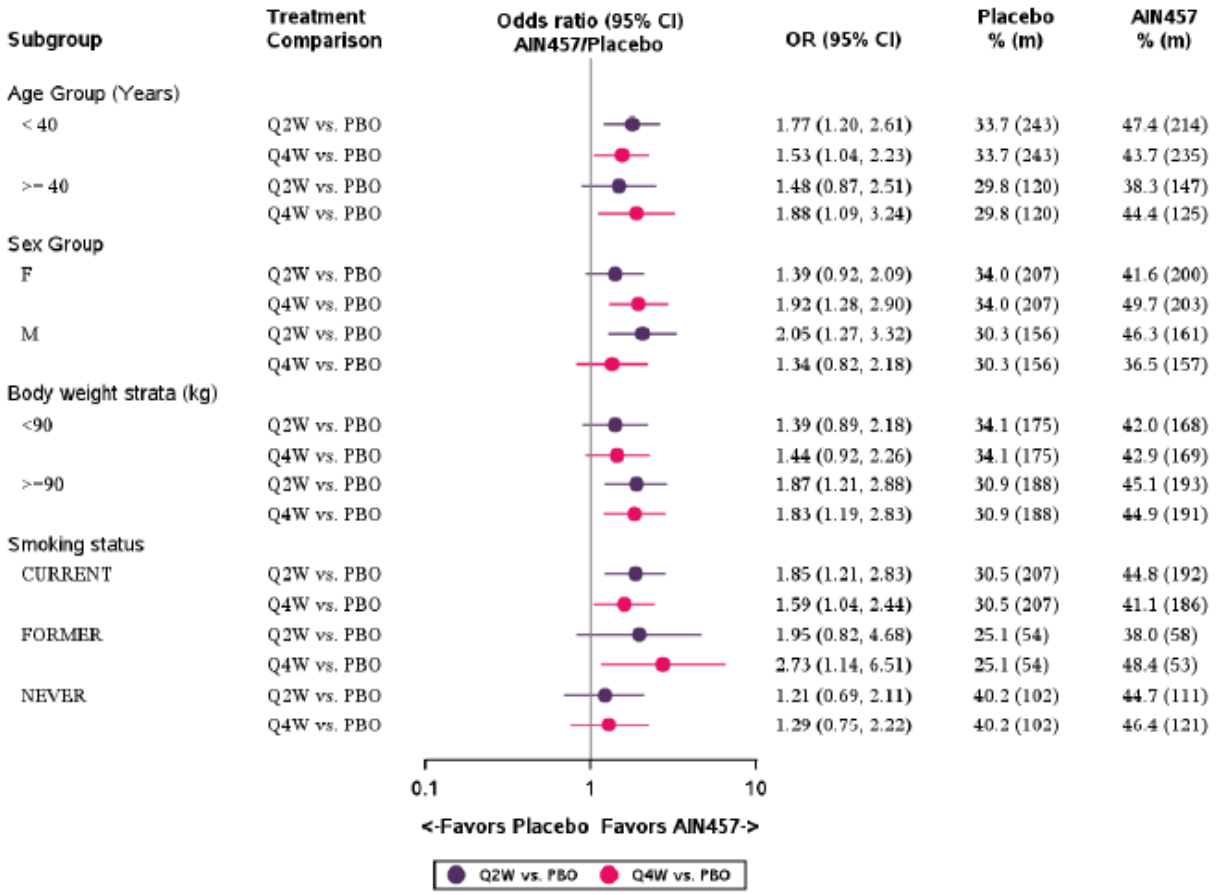
Subgroup analyses for HiSCR50 response at Week 16

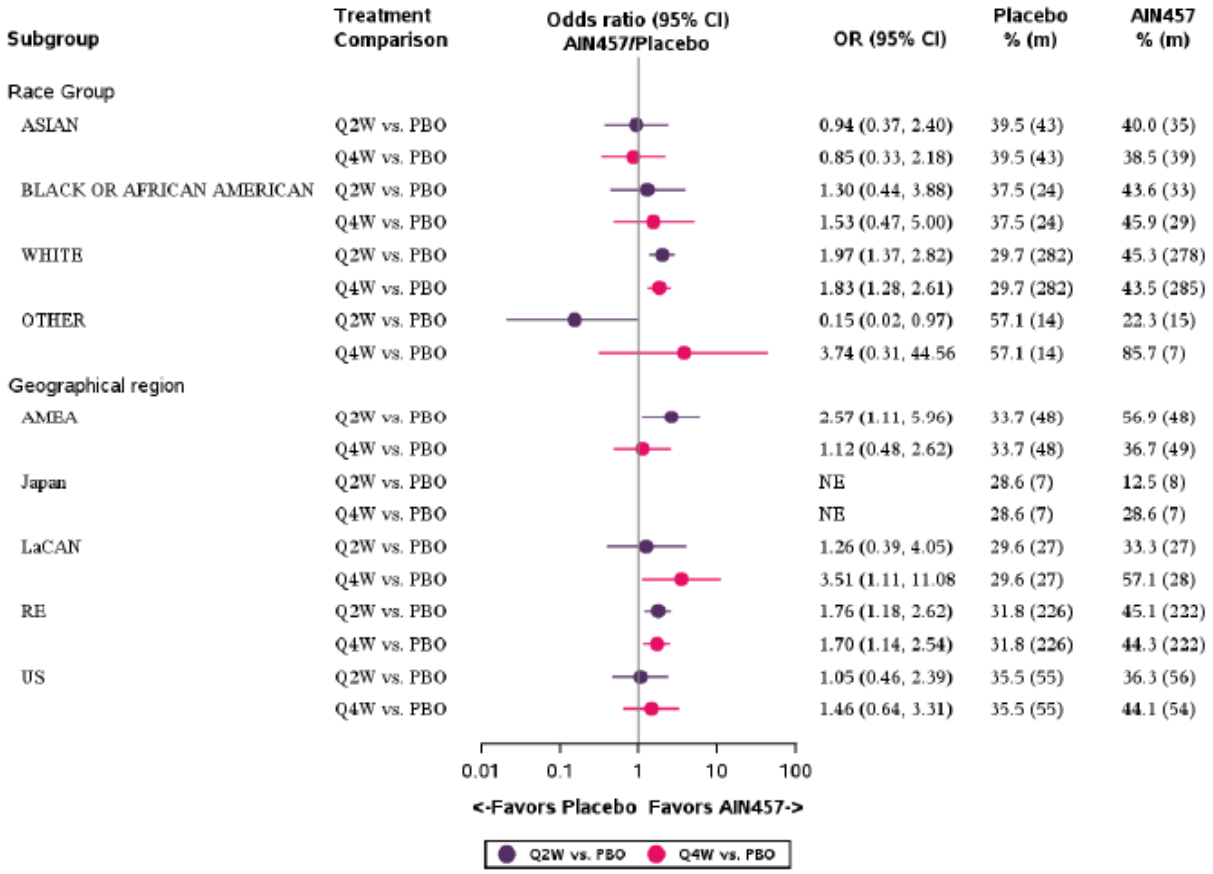
Subgroup analyses using the pooled dataset were performed based on the following factors:

- Age group: <40 years, ≥40 years
- Sex: Female, Male
- Body weight strata: <90 kg, ≥90 kg
- Smoking status: Current, Former, Never
- Race group: Asian, Black or African American, White, Other
- Geographical region: AMEA (Asia-Pacific, Middle East and Africa), Japan, LaCAN (Latin America and Canada), RE (Region Europe), US
- Current antibiotic use: No, Yes
- Disease duration: <2 years, 2 to <5 years, 5 to <10 years, ≥10 years
- Previous exposure to biologics: No, Yes
- Baseline ESR: <20 mm/h, ≥20 mm/h
- Baseline hsCRP levels: <5 mg/L, ≥5-<10 mg/L, ≥10 mg/L
- Baseline AN count： ≤10, >10
- Hurley stage: I, II, III

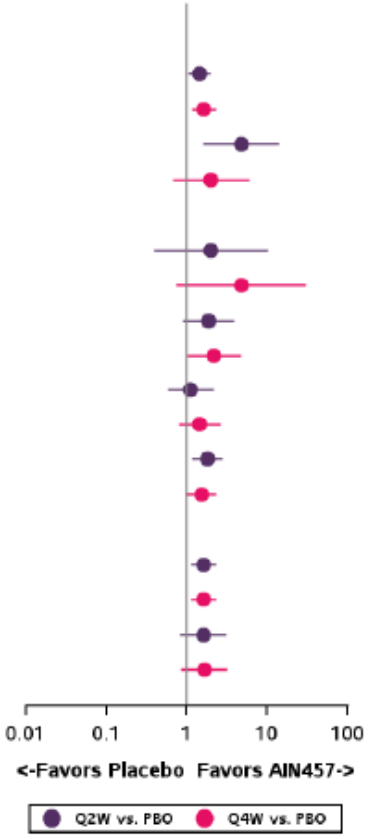
Results of the subgroup analyses for the primary endpoint, HiSCR50 response at Week 16, are displayed in **Figure 31**.

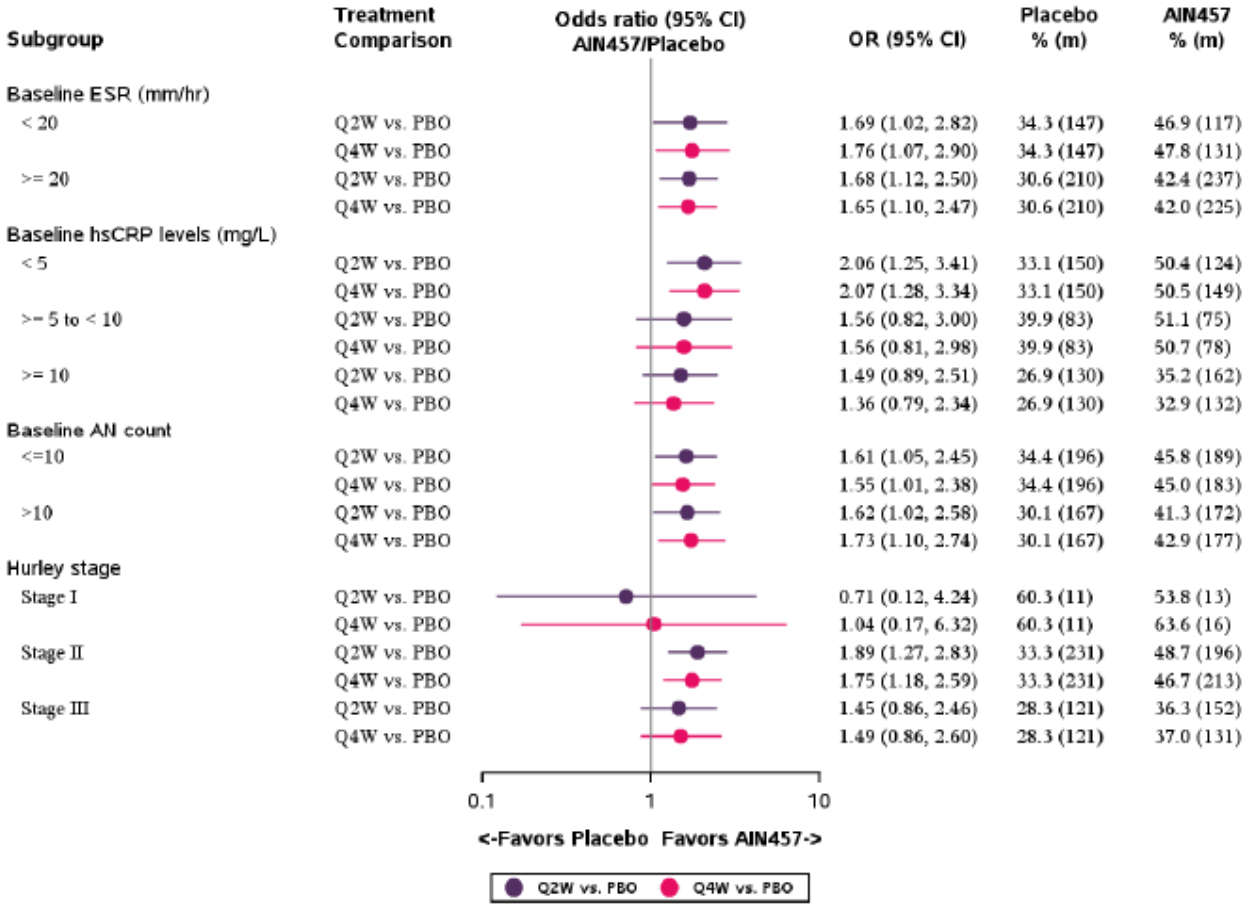
Figure 31 Forest plot of the treatment effect (95% CI) for HiSCR50 response at Week 16 by subgroup (primary estimand, multiple imputation) (pooled data) (Full analysis set)




Subgroup
Treatment Comparison
Odds ratio (95% CI) AIN457/Placebo
OR (95% CI)
Placebo % (m)
AIN457 % (m)
Race Group
ASIAN
Q2W vs. PBO 0.94 (0.37, 2.40) 39.5 (43) 40.0 (35)
Q4W vs. PBO 0.85 (0.33, 2.18) 39.5 (43) 38.5 (39)
BLACK OR AFRICAN AMERICAN
Q2W vs. PBO 1.30 (0.44, 3.88) 37.5 (24) 43.6 (33)
Q4W vs. PBO 1.53 (0.47, 5.00) 37.5 (24) 45.9 (29)
WHITE
Q2W vs. PBO 1.97 (1.37, 2.82) 29.7 (282) 45.3 (278)
Q4W vs. PBO 1.83 (1.28, 2.61) 29.7 (282) 43.5 (285)
OTHER
Q2W vs. PBO 0.15 (0.02, 0.97) 57.1 (14) 22.3 (15)
Q4W vs. PBO 3.74 (0.31, 44.56 57.1 (14) 85.7 (7)
Geographical region
AMEA
Q2W vs. PBO 2.57 (1.11, 5.96) 33.7 (48) 56.9 (48)
Q4W vs. PBO 1.12 (0.48, 2.62) 33.7 (48) 36.7 (49)
Japan
Q2W vs. PBO NE 28.6 (7) 12.5 (8)
Q4W vs. PBO NE 28.6 (7) 28.6 (7)
LaCAN
Q2W vs. PBO 1.26 (0.39, 4.05) 29.6 (27) 33.3 (27)
Q4W vs. PBO 3.51 (1.11, 11.08 29.6 (27) 57.1 (28)
RE
Q2W vs. PBO 1.76 (1.18, 2.62) 31.8 (226) 45.1 (222)
Q4W vs. PBO 1.70 (1.14, 2.54) 31.8 (226) 44.3 (222)
US
Q2W vs. PBO 1.05 (0.46, 2.39) 35.5 (55) 36.3 (56)
Q4W vs. PBO 1.46 (0.64, 3.31) 35.5 (55) 44.1 (54)
0.01
0.1
1
10
100
<-Favors Placebo Favors AIN457->
Q2W vs. PBO
Q4W vs. PBO

Subgroup	Treatment Comparison	OR (95% CI)	Placebo % (m)	AIN457 % (m)
Current antibiotics use				
N	Q2W vs. PBO	1.45 (1.05, 2.01)	34.1 (326)	42.8 (317)
	Q4W vs. PBO	1.64 (1.18, 2.27)	34.1 (326)	45.9 (314)
Y	Q2W vs. PBO	4.78 (1.64, 13.95	18.1 (37)	50.4 (44)
	Q4W vs. PBO	2.01 (0.67, 6.06)	18.1 (37)	30.5 (46)
Disease duration (Years)				
< 2	Q2W vs. PBO	1.98 (0.39, 10.07	30.1 (14)	47.6 (21)
	Q4W vs. PBO	4.75 (0.74, 30.49	30.1 (14)	57.5 (13)
2 - < 5	Q2W vs. PBO	1.87 (0.90, 3.88)	33.4 (71)	48.4 (65)
	Q4W vs. PBO	2.20 (1.02, 4.74)	33.4 (71)	53.3 (53)
5 - < 10	Q2W vs. PBO	1.12 (0.59, 2.14)	38.3 (90)	40.7 (79)
	Q4W vs. PBO	1.46 (0.80, 2.67)	38.3 (90)	47.5 (97)
>= 10	Q2W vs. PBO	1.82 (1.19, 2.80)	29.4 (188)	42.9 (196)
	Q4W vs. PBO	1.51 (0.97, 2.33)	29.4 (188)	38.8 (197)
Previous exposure to biologics				
N	Q2W vs. PBO	1.64 (1.15, 2.33)	34.2 (269)	45.6 (281)
	Q4W vs. PBO	1.61 (1.13, 2.29)	34.2 (269)	45.4 (279)
Y	Q2W vs. PBO	1.60 (0.83, 3.08)	27.3 (94)	37.0 (80)
	Q4W vs. PBO	1.67 (0.86, 3.22)	27.3 (94)	38.8 (81)





- m=number of subjects evaluable.
- Covariates included in the model: treatment group, baseline AN count, weight (excluded in the analysis of the weight subgroup) and study.
- NE=Not Estimable

Source: [SCE Appendix 1-Figure 3.3-1.1]

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28 Summary of Efficacy for trial CAIN457M2301

Title: A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNSHINE)	
Study identifier	Protocol Number: CAIN457M2301 EudraCT Number: 2018-002063-26
Design	Multicenter, randomized, double-blind, placebo controlled, parallel group study

	Duration of main phase: - Treatment Period 1 (TP1): - Treatment Period 2 (TP2): - Post-Treatment follow-up: Duration of Run-in phase: Duration of Extension phase:		 From randomization to Week 16 (pre-dose) From Week 16 (post-dose) to Week 52 8 weeks Not Applicable Not Applicable
Hypothesis	Superiority over placebo at Week 16		
Treatments groups	Secukinumab 300 mg Q2W		Secukinumab 300 mg every 2 weeks. Subcutaneous (s.c.) weekly injections at Weeks 0, 1, 2, 3 and 4 followed by secukinumab 300 mg s.c. injections every 2 weeks until Week 50. N=181
	Secukinumab 300 mg Q4W		Secukinumab 300 mg every 4 weeks. Subcutaneous (s.c.) weekly injections at Weeks 0, 1, 2, 3 and 4 followed by secukinumab 300 mg s.c. injections every 4 weeks until Week 48. N=180
	Placebo		Placebo subcutaneous (s.c.) injections until Week 16 followed by secukinumab 300 mg every 2 weeks or every 4 weeks (after switch to active treatment) after a loading dose of weekly injections at Weeks 16, 17, 18, 19 and 20. N= 180
Endpoints and definitions	Primary endpoint	HiSCR50	Achievement of HiSCR at Week 16. HiSCR is defined as at least a 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae.
	Secondary endpoint	AN count	Percentage change from baseline in AN count at Week 16.
	Secondary endpoint	Flares	Flaring up to Week 16. Flare is defined as at least a 25% increase in AN count with a minimum increase of 2 AN relative to baseline.
	Secondary endpoint	Skin Pain/NRS30	Achievement of NRS30 at Week 16, among subjects with baseline NRS ≥ 3. NRS30 is defined as at least a 30% reduction and at least 2 unit reduction from baseline in Patient's Global Assessment of Skin Pain - at worst.
Database lock	Clinical lock: 8-Nov-2021		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Full analysis set, Week 16. The primary objective was to demonstrate the efficacy of secukinumab compared to placebo with respect to HiSCR50 after 16 weeks of treatment.			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W	Placebo
	Number of subjects	181	180	180
	HiSCR50 (percentage of responders)	45.0	41.8	33.7
	95% confidence interval	(37.8, 52.5)	(34.6, 49.3)	(27.0, 41.2)
Effect estimate per comparison	HiSCR50	Comparison groups	Secukinumab 300 mg Q2W vs. placebo	
		Odds ratio	1.75	
		95% confidence interval	(1.12, 2.73)	
		One-sided P-value	0.0070	
	HiSCR50	Comparison groups	Secukinumab 300 mg Q4W vs. placebo	
		Odds ratio	1.48	
		95% confidence interval	(0.95, 2.32)	
		One-sided P-value	0.0418	
Notes	Odds ratios, associated 95% confidence intervals and P-values are based on a logistic regression model with treatment group, Hurley stage, and baseline AN count, geographical region, use of antibiotics, and baseline body weight (categorized as stratified) as explanatory variable.			
	An estimand with intercurrent events was defined in the SAP for the primary analysis.			
	Multiple imputation was performed to handle missing values.			
	A hierarchical testing procedure was applied where all primary and secondary endpoints were tested in a pre-specified order. The significance level was set to 0.025 one-sided. Unadjusted one-sided p-values are presented.			
Analysis description	**Secondary Analysis** This analysis was pre-specified and part of the testing hierarchy.			
Analysis population and time point description	Full analysis set, Week 16. The secondary objective was to demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to AN count.			
Descriptive statistics and estimate variability	Treatment group	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W	Placebo

	Number of subjects	181	180	180
	AN count (mean percentage change from baseline)	-46.8	-42.4	-24.3
	Standard error	3.33	4.01	4.33

Effect estimate per comparison	AN count	Comparison groups	Secukinumab 300 mg Q2W vs. placebo
		Mean difference between groups	-23.05
		95% confidence interval	(-33.90, -12.21)
		One-sided P-value	<0.0001
	AN count	Comparison groups	Secukinumab 300 mg Q4W vs. placebo
		Mean difference between groups	-18.46
		95% confidence interval	(-29.32, -7.60)
		One-sided P-value	0.0004
Notes	Mean difference, associated 95% confidence intervals and P-values are based on an ANCOVA model with treatment group, Hurley stage, baseline AN counts, geographical region, use of antibiotics, and baseline body weight as explanatory variables.		
	An estimand with intercurrent events was defined in the SAP for the secondary analysis.		
	Multiple imputation was performed to handle missing values.		
	A hierarchical testing procedure was applied where all primary and secondary endpoints were tested in a pre-specified order. The significance level was set to 0.025 one-sided. Unadjusted one-sided p-values are presented.		
Analysis description	**Secondary Analysis** This analysis was pre-specified and part of the testing hierarchy.		
Analysis population and time point description	Full analysis set, Week 16. The secondary objective was to demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to the proportion of patients with HS flares.		

Descriptive statistics and estimate variability	Treatment group	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W	Placebo
	Number of subjects	181	180	180

	Flares (percentage of subjects with flare)	15.4	23.2	29.0
	95% confidence interval	(10.7, 21.6)	(17.4, 30.1)	(22.7, 36.3)

Effect estimate per comparison	Flares	Comparison groups	Secukinumab 300 mg Q2W vs. placebo
		Odds ratio	0.42
		95% confidence interval	(0.25, 0.73)
		One-sided P-value	0.0010
	Flares	Comparison groups	Secukinumab 300 mg Q4W vs. placebo
		Odds ratio	0.71
		95% confidence interval	(0.43, 1.17)
		One-sided P-value	0.0926
Notes	Odds ratios, associated 95% confidence intervals and P-values are based on a logistic regression model with treatment group, Hurley stage, and baseline AN count, geographical region, use of antibiotics, and baseline body weight (categorized as stratified) as explanatory variable.		
	An estimand with intercurrent events was defined in the SAP for the primary analysis.		
	Multiple imputation was performed to handle missing values.		
	A hierarchical testing procedure was applied where all primary and secondary endpoints were tested in a pre-specified order. The significance level was set to 0.025 one-sided. Unadjusted one-sided p-values are presented.		
Analysis description	**Secondary Analysis** This analysis was pre-specified and part of the testing hierarchy.		
Analysis population and time point description	Full analysis set, Week 16. The secondary objective was to demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to proportion of patients with clinical response in HS related skin pain.		

Descriptive statistics and estimate variability	Treatment group	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W	Placebo
	Number of subjects	266	252	251
	Skin Pain/NRS30 response (percentage of responders)	36.6	33.5	23.0
	95% confidence interval	(30.7, 42.8)	(27.5, 40.0)	(17.9, 29.0)

Effect estimate per comparison	Skin Pain/ NRS30	Comparison groups	Secukinumab 300 mg Q2W vs. placebo
		Odds ratio	2.08
		95% confidence interval	(1.37, 3.16)
		One-sided P-value	0.0003
	Skin Pain/NRS30	Comparison groups	Secukinumab 300 mg Q4W vs. placebo
		Odds ratio	1.77
		95% confidence interval	(1.15, 2.70)
		One-sided P-value	0.0044
Notes	Odds ratios, associated 95% confidence intervals and P-values are based on a logistic regression model with treatment group, Hurley stage, and baseline AN count, geographical region, use of antibiotics, baseline body weight (categorized as stratified), and study as explanatory variable. The data of both studies were pooled for this analysis and only subjects with a baseline NRS ≥ 3 are included.		
	An estimand with intercurrent events was defined in the SAP for the primary analysis.		
	Multiple imputation was performed to handle missing values.		
	A hierarchical testing procedure was applied where all primary and secondary endpoints were tested in a pre-specified order. The significance level was set to 0.025 one-sided. Unadjusted one-sided p-values are presented.		

Table 29 Summary of efficacy for trial CAIN457M2302

Title: A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNRISE)		
Study identifier	Protocol Number: CAIN457M2302 EudraCT Number: 2018-002062-39	
Design	Multicenter, randomized, double-blind, placebo controlled, parallel group study	
	Duration of main phase: - Treatment Period 1 (TP1): - Treatment Period 2 (TP2): - Post-Treatment follow-up: Duration of Run-in phase: Duration of Extension phase:	 From randomization to Week 16 (pre-dose) From Week 16 (post-dose) to Week 52 8 weeks Not Applicable Not Applicable
Hypothesis	Superiority over placebo at Week 16	

Treatments groups	Secukinumab 300 mg Q2W		Secukinumab 300 mg every 2 weeks. Subcutaneous (s.c.) weekly injections at Weeks 0, 1, 2, 3 and 4 followed by secukinumab 300 mg s.c. injections every 2 weeks until Week 50. N=180
	Secukinumab 300 mg Q4W		Secukinumab 300 mg every 4 weeks. Subcutaneous (s.c.) weekly injections at Weeks 0, 1, 2, 3 and 4 followed by secukinumab 300 mg s.c. injections every 4 weeks until Week 48. N=180
	Placebo		Placebo subcutaneous (s.c.) injections until Week 16 followed by secukinumab 300 mg every 2 weeks or every 4 weeks (after switch to active treatment) after a loading dose of weekly injections at Weeks 16, 17, 18, 19 and 20. N= 183
Endpoints and definitions	Primary endpoint	HiSCR50	Achievement of HiSCR at Week 16. HiSCR is defined as at least a 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae.
	Secondary endpoint	AN count	Percentage change from baseline in AN count at Week 16.
	Secondary endpoint	Flares	Flaring up to Week 16. Flare is defined as at least a 25% increase in AN count with a minimum increase of 2 AN relative to baseline.
	Secondary endpoint	Skin Pain/NRS30	Achievement of NRS30 at Week 16, among subjects with baseline NRS ≥ 3. NRS30 is defined as at least a 30% reduction and at least 2 unit reduction from baseline in Patient's Global Assessment of Skin Pain - at worst.
Database lock	Clinical lock: 30-Oct-2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set, Week 16. The primary objective was to demonstrate the efficacy of secukinumab compared to placebo with respect to HiSCR50 after 16 weeks of treatment.		

Descriptive statistics and estimate variability	Treatment group	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W	Placebo
	Number of subjects	180	180	183
	HiSCR50 (percentage of responders)	42.3	46.1	31.2

	95% confidence interval	(35.2, 49.8)	(38.8, 53.7)	(24.7, 38.4)

Effect estimate per comparison	HiSCR50	Comparison groups	Secukinumab 300 mg Q2W vs. placebo
		Odds ratio	1.64
		95% confidence interval	(1.05, 2.55)
		One-sided P-value	0.0149
	HiSCR50	Comparison groups	Secukinumab 300 mg Q4W vs. placebo
		Odds ratio	1.90
		95% confidence interval	(1.22, 2.96)
		One-sided P-value	0.0022

Notes	Odds ratios, associated 95% confidence intervals and P-values are based on a logistic regression model with treatment group, Hurley stage, and baseline AN count, geographical region, use of antibiotics, and baseline body weight (categorized as stratified) as explanatory variable.
	An estimand with intercurrent events was defined in the SAP for the primary analysis.
	Multiple imputation was performed to handle missing values.
	A hierarchical testing procedure was applied where all primary and secondary endpoints were tested in a pre-specified order. The significance level was set to 0.025 one-sided. Unadjusted one-sided p-values are presented.
Analysis description	**Secondary Analysis** This analysis was pre-specified and part of the testing hierarchy.
Analysis population and time point description	Full analysis set, Week 16. The secondary objective was to demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to AN count.

Descriptive statistics and estimate variability	Treatment group	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W	Placebo
	Number of subjects	180	180	183
	AN count (mean percentage change from baseline)	-39.3	-45.5	-22.4
	Standard error	4.43	4.08	4.84

Effect estimate per comparison	AN count	Comparison groups	Secukinumab 300 mg Q2W vs. placebo

		Mean difference between groups	-16.33
		95% confidence interval	(-28.79, -3.88)
		One-sided P-value	0.0051
	AN count	Comparison groups	Secukinumab 300 mg Q4W vs. placebo
		Mean difference between groups	-22.94
		95% confidence interval	(-35.24, -10.63)
		One-sided P-value	0.0001
Notes	Mean difference, associated 95% confidence intervals and P-values are based on an ANCOVA model with treatment group, Hurley stage, baseline AN counts, geographical region, use of antibiotics, and baseline body weight as explanatory variables.		
	An estimand with intercurrent events was defined in the SAP for the secondary analysis.		
	Multiple imputation was performed to handle missing values.		
	A hierarchical testing procedure was applied where all primary and secondary endpoints were tested in a pre-specified order. The significance level was set to 0.025 one-sided. Unadjusted one-sided p-values are presented.		
Analysis description	**Secondary Analysis** This analysis was pre-specified and part of the testing hierarchy.		
Analysis population and time point description	Full analysis set, Week 16. The secondary objective was to demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to the proportion of patients with HS flares.		

Descriptive statistics and estimate variability	Treatment group	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W	Placebo
	Number of subjects	180	180	183
	Flares (percentage of subjects with flare)	20.1	15.6	27.0
	95% confidence interval	(14.7, 26.7)	(10.9, 21.7)	(20.9, 34.1)

Effect estimate per comparison	Flares	Comparison groups	Secukinumab 300 mg Q2W vs. placebo
		Odds ratio	0.68
		95% confidence interval	(0.41, 1.14)
		One-sided P-value	0.0732

	Flares	Comparison groups	Secukinumab 300 mg Q4W vs. placebo
		Odds ratio	0.49
		95% confidence interval	(0.29, 0.84)
		One-sided P-value	0.0049
Notes	Odds ratios, associated 95% confidence intervals and P-values are based on a logistic regression model with treatment group, Hurley stage, and baseline AN count, geographical region, use of antibiotics, and baseline body weight (categorized as stratified) as explanatory variable.		
	An estimand with intercurrent events was defined in the SAP for the primary analysis.		
	Multiple imputation was performed to handle missing values.		
	A hierarchical testing procedure was applied where all primary and secondary endpoints were tested in a pre-specified order. The significance level was set to 0.025 one-sided. Unadjusted one-sided p-values are presented.		
Analysis description	**Secondary Analysis** This analysis was pre-specified and part of the testing hierarchy.		
Analysis population and time point description	Full analysis set, Week 16. The secondary objective was to demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to proportion of patients with clinical response in HS related skin pain.		

Descriptive statistics and estimate variability	Treatment group	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W	Placebo
	Number of subjects	266	252	251
	Skin Pain/NRS30 response (percentage of responders)	36.6	33.5	23.0
	95% confidence interval	(30.7, 42.8)	(27.5, 40.0)	(17.9, 29.0)

Effect estimate per comparison	Skin Pain/NRS30	Comparison groups	Secukinumab 300 mg Q2W vs. placebo
		Odds ratio	2.08
		95% confidence interval	(1.37, 3.16)
		One-sided P-value	0.0003
	Skin Pain/NRS30	Comparison groups	Secukinumab 300 mg Q4W vs. placebo
		Odds ratio	1.77
		95% confidence interval	(1.15, 2.70)

		One-sided P-value	0.0044
Notes	Odds ratios, associated 95% confidence intervals and P-values are based on a logistic regression model with treatment group, Hurley stage, and baseline AN count, geographical region, use of antibiotics, baseline body weight (categorized as stratified), and study as explanatory variable. The data of both studies were pooled for this analysis and only subjects with a baseline NRS ≥ 3 are included.		
	An estimand with intercurrent events was defined in the SAP for the primary analysis.		
	Multiple imputation was performed to handle missing values.		
	A hierarchical testing procedure was applied where all primary and secondary endpoints were tested in a pre-specified order. The significance level was set to 0.025 one-sided. Unadjusted one-sided p-values are presented.		

2.4.3. Discussion on clinical efficacy

The variation application is supported by two identical Phase 3 studies, M2301 and M2302.

As part of the initial submission, the MAH submitted Week 16 interim clinical study reports for both studies, with Week 52 data being included for some 65% of subjects. Additional data based on the full 52-week datasets were provided at the CHMP request.

No separate dose response or PK studies were conducted in HS patients to confirm the assumptions made in dose selection for the main studies, although this was recommended in SA by the CHMP. The assumptions concerning a higher mean exposure being achieved with the Q2W regimen have however been confirmed through PK assessments within the main studies.

Design and conduct of clinical studies

Design

The design of the studies is quite straightforward and is considered adequate to meet the primary aims of the development programme. In light of the expected substantial placebo response rate, the use of a placebo control arm is considered essential. Furthermore, the lack of an active control arm was considered acceptable in the SA procedure. A total treatment period of 52 weeks is considered sufficient for safety assessment purposes and also enables assessment of maintenance of effect.

According to the MAH, the use of placebo as a comparative agent was limited to 16 weeks due to the severity of the disease requiring medical therapy and, hence, ethical concerns of keeping subjects with HS on placebo. On the other hand, the CHMP in the SA procedure highlighted the considerable placebo response rate observed in previous adalimumab studies in HS. The CHMP therefore considered that a placebo control beyond 16 weeks could be feasible with appropriate escape/rescue criteria and also recommended incorporating a randomised withdrawal design since the question on cessation and/or dose reduction would be an issue of interest. The MAH was requested to further justify its choice of study design beyond Week 16 and discuss how the open questions regarding most appropriate long-term treatment strategies will be addressed. In the response, the MAH indicated that these issues are being addressed in the currently ongoing extension study M2301E1, evaluating the effect of treatment interruption (randomised withdrawal) and re-treatment with secukinumab on efficacy, tolerability and

safety in subjects with moderate to severe HS who completed either of the two Phase 3 studies, M2301 or M2302. The CHMP recommends the MAH to submit these results for assessment once they become available. According to the MAH, primary endpoint analysis of the extension study will be conducted on data collected at Week 104 and is currently estimated for H2 2023.

In principle, the eligibility criteria were consistent with the proposed indication. Hurley staging was not directly used in subject selection; the disease severity of moderate to severe was defined as having a total of at least 5 inflammatory lesions, i.e., abscesses and/or inflammatory nodules, affecting at least 2 distinct anatomic areas. This definition focuses on the degree and extent of inflammatory activity at baseline instead of using the level of scarring in the worst affected area (as in the previously used Hurley stages). Consistent with this definition, the majority of the study population was still expected to be in Hurley stages II and III, with only a small proportion of subjects in Hurley stage I. The justification is acknowledged, and the statement "moderate to severe" in the proposed indication wording is considered appropriately covered by the CHMP.

Contrary to the CHMP SA recommendation, previous treatment failure to antibiotics was not a requirement to enter the study. The MAH justified the deviation on the assumption that the majority of patients entering the study would be expected to have previously received systemic antibiotics at least during the period since diagnosis ($\geq$ 1 year). Reflecting the clinical practice in many countries and the concern of exposing some patients to placebo for up to 16 weeks without anti-inflammatory therapy, the MAH also decided to allow a proportion of the patients to remain on a stable dose of systemic antibiotics during Treatment Period 1. Information on the previous use of systemic therapies at baseline was collected, confirming that over 80% of subjects had previously received systemic antibiotics for HS, with lack of efficacy reported as the most frequent reason for discontinuation. Subgroup analyses based on previous antibiotic use were also provided as part of the documentation. It is furthermore noted that the proposed indication foresees use in patients who have not responded adequately to conventional systemic HS therapy, thereby placing secukinumab into second-line use. The proposed positioning is considered appropriate in light of the population enrolled into the studies, and the deviation from SA is considered sufficiently addressed by the MAH.

All subjects are dosed with PFS every other week. From the perspective of experimental setting, the placebo group does not represent a realistic real-life treatment strategy but, instead, it reflects the outcomes of a secukinumab 300 mg Q2W treatment in the hypothetical scenario where secukinumab 300 mg has no pharmacological effect on HS outcomes. The injection schedule of secukinumab 300 mg Q4W arm was matched with that of secukinumab 300 mg Q2W and the former represents hypothetical outcomes of secukinumab 300 mg Q2W treatment where the pharmacological activity of every other dose (following loading doses) is eliminated. The setting is ideal for evaluating whether outcomes are improved by biweekly dosing of secukinumab as compared with dosing every 4 weeks although comparison of Q2W and Q4W regimens is not among pre-planned study objectives. The re-randomisation, at Week 16, of subjects that initially received placebo only is considered to provide additional data to allow comparison of the Q2W and Q4W dose regimens to induce and maintain improvements in HS outcomes.

Concomitant use of systemic antibiotics (tetracycline up to 500 mg b.i.d., minocycline up to 100 mg b.i.d., and doxycycline up to 100 mg b.i.d.) was allowed for the subjects entered in the antibiotics strata provided that the dose was kept stable until Week 16. Topical antibiotics were prohibited from all subjects through to Week 16. This is considered appropriate to ensure comparability of the randomised treatments.

The primary signs and symptoms of HS are abscesses, inflammatory nodules or draining fistulas and these are assessed by the HiSCR. HiSCR has been used as the primary endpoint for demonstrating clinical efficacy of adalimumab and was also endorsed (in fact recommended in favour of a modified definition

proposed by MAH) by the CHMP in the SA. As such, the HiSCR is considered an acceptable primary endpoint.

As evidenced by sometimes large variability in the number and types of HS lesions reported between screening and baseline visits, and variability during the placebo treatment, disease activity may fluctuate rapidly. Also, the assessment (counting) of each type of manifestation can be assumed to be a source of variability. For these reasons, achievement of HiSCR at any point in time cannot be interpreted as individual patients having benefited from the treatment. Instead, HiSCR response should be considered as one of many potential ways of way of summarising data concerning the time course of joint distribution of various lesion types into a comprehensible measure.

The MAH justified the selection of other endpoints as reflecting the most important domains of HS and providing complementary clinically relevant information not fully evaluated in the primary endpoint. While the AN count is in fact a part of the HiSCR score, treating the count as a quantitative variable can be agreed to provide additional insight. It is also agreed that flares and pain are clinically relevant aspects of HS that are not captured with the primary endpoint. As such, and in the absence of any disease-specific regulatory guidance, the MAH's selection of endpoints is overall endorsed.

Methodological aspects

Patients that discontinued treatment due to LoE or AE (as based on the treatment withdrawal CRF) were considered as non-responders, while other treatment discontinuations led to censoring of affected data and were multiple imputed following a hypothetical scenario where treatment was not discontinued. The handling of intercurrent events suggests a somewhat hypothetical interpretation to the primary analysis: outcome if randomised treatment is continued up to week 16 and no rescue medication were used (assuming that those requiring rescue medication would have failed HiSCR50 at Week 16) allowing the use of non-rescue medications. A supplementary estimand focuses on Week 16 outcomes regardless of whether randomised treatment was discontinued and, as such, corresponds to an ITT analysis. However, all subjects who discontinued the study treatment also discontinued the study implying that no substantial difference could exist in the results and their interpretation of the primary and supplementary estimand and, therefore, no statements should be made about result robustness based on the similarity of the two analyses.

For the primary estimand, the majority of missing data were imputed under MAR, i.e., according to the scenario that the subject remained on the randomized treatment. The principle of reference-based imputation, adopted for certain intercurrent events, where missing data related to the ICEs were modeled as adopting a trajectory of the placebo arm following ICE, is appropriate especially for handling treatment discontinuations for the supplementary estimand. Reference-based imputation can be considered somewhat conservative for the primary estimand and, as such, acceptable.

Multiple imputation of HiSCR response and AN count were implemented at the level of the underlying quantitative components, for each component separately. The technique used appears to presume that the components of HiSCR are inter-independent, e.g., that reduction in inflammatory nodules is not informative about concurrent or future reduction of abscesses. The MAH was therefore requested to comment on the assumptions and evaluate its appropriateness among the observed data. In response to the RSI, the MAH clarified that the manifestations are 'not necessarily correlated' and provided some data to support this assumption. The principled concerns about the multiple imputation procedure were not fully resolved by the MAH's response. However, considering the relatively small proportion of imputed data (especially those with multiple visits missed prior to Week 16) and the stated level of correlation between the components, the potential bias to the overall result from this methodological detail alone is likely to be small.

A tipping analysis was included that explored how many subjects with missing HiSCR evaluation but who were multiple imputed as responders need to be switched to non-responders to lose statistical significance in the comparison with placebo arm. The p-values appear very insensitive to the number of switches. This is probably so because what is shown as the number of switchers appears to indicate the maximum number of switches across the 100 multiple imputed datasets rather than actual difference in the number of imputed responders. In this respect, the available tipping point analysis is considered uninformative and even misleading.

Randomisation was stratified by geographic region, concomitant antibiotic use and body weight. Each of these stratification factors are considered to have their own independent rationale, and it is considered reasonable to use statistical models that address the stratification factor's effects by inclusion of a regression parameter corresponding to the level of each stratification factor. Indeed, the MAH used logistic regression with the stratification effects as explanatory variables.

An elegant, graphically illustrated algorithm was prespecified to ensure that familywise type-I-error rate does not exceed 2.5%. The hypothesis testing strategy is considered to be clinically meaningful and statistically adequate to control the rate of false positive findings. However, an unequal initial allocation of alpha was specified as part of protocol amendment 2: 0.02 for the Q2W regimen and 0.005 for the Q4W regimen, reflecting MAH's expectation of better efficacy of Q2W. Unequal allocation of alpha is considered acceptable if the decision to do so was not affected by the results. However, an interim analysis for futility and efficacy was planned when approximately 40% of the subjects in M2301 and M2302 had completed Week 16. In response to the RSI, the MAH explained that neither the futility criterion nor the iDMC conveyed any information regarding relative benefit of the different treatment arms and detailed "emerging external data" that increased the expectation for the Q2W dosing relative to Q4W.

The appropriateness of the statistical methods for the long-term data appears questionable and partly unclear. In particular, the difficulty in interpreting observed case analyses of long-term follow-up studies are well recognized. Although the methodological details of the longitudinal logistic regression model are partly unclear it is agreed that such a method is helpful in assessing maintenance of effect in terms of HiSCR50 response (but not so for cumulative flare rate) especially when evaluated together with the MMRM for the more quantitative AN count.

Study conduct

The original protocols for both studies had an effective date of 07 August 2018. First subject first visits took place on 31 January 2019 for M2301, and on 25 February 2019 for M2302. Data cut-offs for the Week 16 analyses took place on 01 October 2021 for M2301, and on 23 September 2021 for M2302. The studies were conducted across a geographically diverse selection of countries. EU Member States were well represented, with substantial numbers of subjects enrolled e.g. in France and Germany.

The study protocol was amended on two occasions. The first amendment was implemented primarily to address emerging COVID 19 -related challenges in study conduct. Amendment 2 adjusted the statistical testing strategy due to emerging external data. Overall, the amendments can be considered adequately justified and do not jeopardise the reliability or integrity of the study. A serious GCP violation was reported for 2 subjects in study M2301, but these have been adequately described and managed and do not raise further concern.

Disposition and baseline characteristics

A high proportion of subjects completed Treatment Period 1 in both studies, and there was no particular clustering with respect to reasons for discontinuation. Over the entire study period, attrition remained moderate, with most of the discontinuations being attributed to an unsatisfactory treatment effect. Across both studies, the number of subjects discontinuing due to an adverse event was quite low, which is consistent with experience from secukinumab studies in other indications. Overall, no relevant differences are noted between the studies as regards subject disposition.

As acknowledged by the MAH, many of the study and treatment discontinuations whose primary reason was reported as being subject decision were further specified as being related to lack of satisfactory treatment response. The MAH was therefore requested to provide a summary of discontinuation reasons that more realistically reflects the proportion of patients that discontinued due to lack of efficacy and recategorizes other cases, as appropriate, to meaningful groups based on further specification of discontinuation reason. In its response, the MAH provided further clarification regarding the categorisation, and while the categorisation principles cannot be completely agreed, the limited number of subjects discontinuing due to an unsatisfactory treatment response does not warrant further concerns about the robustness of the overall conclusions in the current studies, particularly as they relate to the primary efficacy analyses at Week 16. As such, the issue is not pursued further.

Mean age at baseline was about 36 years, and very few subjects aged 65 years or above were enrolled. About 56% of subjects were female, and almost 80% were White. Almost 70% were either current or former smokers. Mean BMI was about 32 kg/m^2.

Consistent with the MAH's expectations, the vast majority of subjects were Hurley stage II or III, and the sample sizes for both are sufficient to justify the statement "moderate to severe HS" in the proposed indication. Previous exposure to adalimumab was reported for 22% of subjects (total N=238), permitting a reasonable assessment of efficacy in this subpopulation. Furthermore, previous exposure to systemic antibiotics was reported for over 80% of subjects; as such, the enrolled population can in practice be considered similar to that targeted by the CHMP's recommendation of only including subjects with a history of failure to antibiotic therapy.

Efficacy data and additional analyses

At Week 16, both secukinumab dosing regimens showed numerically greater HiSCR50 response rates compared to placebo; in study M2302, the result was statistically significant for both regimens (Q2W vs placebo: 42.3% vs. 31.2%, p=.0149; Q4W vs placebo: 46.1% vs. 31.2%, p=.0022), whereas in M2301, the result for Q4W vs. placebo was not statistically significant (Q2W vs placebo: 45.0% vs. 33.7%, p=.0070; Q4W vs placebo: 41.8% vs. 33.7%, p=.0418). It should however be noted that in M2301, the difference in response rates between the Q2W and Q4W regimens was only 3 percentage points, and in M2302, the treatment difference vs. placebo was numerically larger for the Q4W regimen than the Q2W regimen. Results on sensitivity analyses and supplementary analyses, as presented, are consistent with the primary analysis. As such, the short-term efficacy has in principle been adequately demonstrated.

The magnitude of the treatment effect (about 11 percentage points for both regimens vs. placebo in the pooled data) can be considered quite modest. Recognising the inherent difficulties in indirect comparison of studies, the treatment effect of secukinumab may be somewhat smaller than observed in the previously conducted adalimumab studies. However, when contextualised with the dearth of currently available therapies, the observed effect is still considered clinically meaningful by the CHMP.

This notwithstanding, it is not clear that the Q2W can be considered to unequivocally outperform the Q4W regimen. As noted above, the supposedly identical trials provide conflicting results for the two regimens as regards the treatment difference vs. placebo. The MAH has argued that a more severe

population was enrolled by chance into the Q2W group, but the post-hoc analysis, in which additional covariates reflecting disease severity were included, remains largely consistent with the primary analysis.

Given the identical loading scheme from Week 0 to Week 4 in the Q2W and Q4W regimens and in light of differences in observed treatment response at Week 4, additional analyses were also provided to elucidate the development of treatment response from Week 4 until Week 16. While the additional analyses show some support for a greater increase in response in the Q2W regimen compared to the Q4W regimen, it is still noted that in M2302, the calculated OR remains close to 1 and an added benefit can therefore not be concluded.

In light of the small and inconclusively demonstrated incremental gain in average response, the CHMP did not agree to the MAH's initial proposal of recommending the higher Q2W maintenance dose for every patient. Instead, an escalation strategy in patients with an insufficient response, similar to that already authorised for several other indications, was recommended, even when recognising that it had not been directly studied in HS patients. The MAH agreed to amend the posology accordingly (see section 2.3.4 Discussions on clinical pharmacology).

Results on AN count were consistent with HiSCR data, with a larger decrease from baseline observed with both secukinumab regimens compared to placebo. In M2301, the decrease was larger with Q2W compared to Q4W (Q2W vs placebo: -46.8 vs. -24.3, p <.0001; Q4W vs placebo: -42.4 vs. -24.3, p=.0004), whereas the opposite was true in M2302 (Q2W vs placebo: -39.3 vs. -22.4, p=.0051; Q4W vs placebo: -45.5 vs. -22.4, p=.0001). With respect to flare rate, the increase from Week 4 to Week 16 was smaller for the secukinumab Q2W dose regimen compared to the secukinumab Q4W dose regimen in both studies (M2301: 5.9% for Q2W vs 11.7% for Q4W; M2302: 8.7% for Q2W vs 9.2 for Q4W).

Pre-planned statistical analyses for NRS30 response were limited to subjects with a baseline NRS ≥3 and using pooled data only (Q2W vs placebo: 36.6% vs. 23.0%, p=.0003; Q4W vs placebo: 33.5% vs. 23.0%, p=.0044). Although the difference to placebo was statistically significant only for the Q2W regimen, the numerical differences to placebo were quite similar for both secukinumab regimens, with a difference of 3 percentage points in favour of the Q2W regimen. However, within the study-level data, it is interesting to note that for M2031, in which e.g., HiSCR50 response rates were quite similar between the secukinumab groups, the Q2W regimen performed unexpectedly poorly, whereas in M2302, in which the Q4W clearly outperformed Q2W e.g., on HiSCR50 response, the Q2W regimen was numerically slightly better than the Q4W regimen. This does not seem consistent with the MAH's claim that the estimate of treatment effect for the Q2W regimen is reduced by a more severe population having been enrolled into that treatment group particularly in study M2302.

A requested post-hoc analysis of NRS data in the FAS showed larger decreases in mean NRS for both secukinumab regimens compared to placebo.

Both secukinumab regimens decreased inflammatory markers (hsCRP and ESR) compared to placebo, with slightly greater effect with Q2W. Decreases on DLQI total score were also larger with both secukinumab regimens compared to placebo; in M2302, the DLQI response rate seen with Q4W was greater than with Q2W. Presentation of results for exploratory endpoints that are analysed outside of the multiplicity-controlled testing framework is generally not acceptable in the SmPC, and the MAH was initially requested to delete all data related to exploratory endpoints from section 5.1 of the SmPC unless a particular justification can be provided. In its response, the MAH further argued that data on health-related quality of life outcomes would be of high relevance to prescribers and requested retention of the data in the SmPC. A very limited presentation was finally agreed by the CHMP.

Based on analyses of observed data, HiSCR50 response rates achieved by week 16 were maintained and even improved further until Week 52, although potential biases related to analyses based on observed data should be recognised. Consistent with the interim results, there was overall very little difference in

long-term response rates between the two secukinumab regimens; thus, the long-term results are also supportive of a posology that starts with a Q4W maintenance regimen.

The HiSCR shift table provided by the MAH, based on the subpopulation of subjects for whom both Week 16 and Week 52 values were available, also indicates that the majority of subjects in either group receiving secukinumab from Week 0 and developing a HiSCR50 response by Week 16 maintained their response until Week 52; furthermore, a large proportion of Week 16 non-responders became responders by Week 52. Among the subjects switching from placebo to secukinumab at Week 16, some 45% of placebo non-responders developed a response by Week 52; this response rate is in fact well aligned with the 44% response rate observed with secukinumab from Week 0 to Week 16. Interestingly, among the Week 16 placebo responders, the majority maintained their response until Week 52. Nevertheless, the inherent biases in the subpopulation available for this analysis have to be recognised.

At the CHMP request, results based on the full 52-week dataset were provided. Overall, the newly provided results do not raise further concern related to maintenance of effect until Week 52.

Subgroup analyses based on a number of demographic and baseline characteristics quite consistently demonstrated effects favouring secukinumab over placebo. However, none of the subgroup analyses demonstrate convincing effects favouring Q2W over Q4W.

With respect to the proposed indication, it is noted that consistent effects were seen between Hurley stages II and III; it is thereby agreed that the indication can cover patients with moderate to severe HS. It is understood that the proposed indication "moderate to severe" is likely to be interpreted as referring to Hurley stages II and III and can thereby be justified. While neither of the secukinumab regimens showed efficacy vs placebo among subjects with Hurley stage I, the very small sample size is recognised; in any case, Hurley stage I would in clinical practice likely be considered as mild disease and thereby not be covered by the proposed indication. Even though the sample size for subjects with previous exposure to biologics is somewhat limited, no concerning trend that should limit use among biologic-experienced patients can be seen. Additionally, the MAH was requested to include the world "active" in the indication as a qualifier for disease state. The MAH agreed and updated the indication wording to include the word "active" in it.

Following an FDA inspection, the MAH identified data discrepancies for the NRS30 / Skin pain endpoint (secondary endpoint), impacting both studies CAIN457M2301 and CAIN457M2302; specifically, due to a human error, the variables "average pain" and "worst pain" were inadvertently transposed at the time of the creation of the Study Data Model Tabulation (SDTM) datasets, resulting in the incorrect NRS pain variable used for the analysis of the NRS30 / Skin pain endpoint. The MAH was requested to fully complete all of the planned data quality checks for the dossier supporting the registration of the HS indication and provide adequate confirmation that all data are correct and that no further updates are required, before a final opinion could be adopted. The MAH provided the requested confirmation and updated documentation.

2.4.4. Conclusions on the clinical efficacy

In two studies conducted in subjects with moderate to severe HS, secukinumab demonstrated efficacy vs. placebo on the primary endpoint of HiSCR50 response rate at Week 16; consistently greater effects vs. placebo were also seen on secondary endpoints. Descriptive Week 52 data are supportive of adequate maintenance of effect. The long term effect will be further studied in the ongoing extension study M2301E1. The CHMP recommends the MAH to submit these results for assessment once they become available

The size of the treatment effect, while quite modest, can be considered clinically relevant. However, numerical differences between the studied Q2W and Q4W maintenance regimens were generally very small, and the MAH therefore agreed to a posology whereby the Q4W maintenance regimen would be considered standard and an increase to Q2W could be considered based on evaluation of clinical response on the standard regimen.

The CHMP concluded that the efficacy data available supports the following indication :

Cosentyx is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy (see section 5.1).

2.5. Clinical safety

Introduction

The main safety data in support of the extension of indication of secukinumab to moderate to severe HS come from the two randomized, double-blind, multicenter phase 3 studies of identical design, study M2301 and study M2302, assessing two subcutaneous secukinumab dose regimens (300 mg Q2W or Q4W). Pooled data are presented to assess 16 week short-term (Treatment Period 1) and 52-week long-term safety data (Entire Study Period) up to the data cut-off dates (01 October 2021 for Study M2301 and 23 September 2021 for Study M2302). Safety data for at least 16 weeks of treatment are available for all subjects. Interim long-term data up to 52-weeks was initially available for 59,1 % of the randomised patients. Subsequently, full 52-week long-term safety data was made available.

The population enrolled in Studies M2301 and M2302 consisted of subjects with moderate to severe HS, aged ≥18 years who had a diagnosis of HS ≥1 year prior to baseline (see efficacy section for details).

In addition, as the Q2W administration of secukinumab 300 mg has recently been approved for adult patients ≥90 kg with moderate to severe psoriasis in the EU, based on study A2324, a comparison of available safety data was performed to present findings from psoriasis and HS.

Furthermore, the, to date, existing secukinumab safety database across all indications, with a cumulative exposure of 34,907.50 subject-years from 20,961 subjects and healthy volunteers in clinical studies, and 680,470 subject-years of post-marketing exposure to secukinumab (AIN457 PSUR 26-Dec-2019 to 25-Dec-2020) is also referred to.

Safety evaluations consisted of frequency of AEs and SAEs, laboratory abnormalities, vital signs, important identified and potential risks including Infections, Hypersensitivity, Malignant or unspecified tumours, Suicidal ideation and behaviour, MACE and Hepatitis B reactivation, and other safety topics of interest, including Neutropenia, IBD and Candida infections. Given the substantial impact of the COVID-19 pandemic on the recruitment and timelines of Studies M2301 and M2302, COVID-19 was also considered a safety topic of interest.

All safety analyses were based on the Safety Set. The **Safety Set** included all subjects who received at least one dose of study treatment. Three subjects in Study M2301 (1 mis-randomized in IRT, 1 subject with severe GCP violation, and 1 subject with serious breach) and 1 subject in Study M2302 (mis-randomized in IRT) were excluded from the Safety set as per definition.

Patient exposure

In **Treatment Period 1**, the duration of exposure was similar across all treatment groups, with >97% of subjects exposed to treatment for at least 12 weeks and a median exposure of 112 days.

Entire Study Period

Initial interim (approx. 60% of patients) 52-week safety subset

Exposure to study treatment was summarized for the pooled data (Safety set) from both of the phase 3 studies. The overall subject exposure during the 52-week Entire Study Period (up to the data cut-off dates for Studies M2301 and M2302) to secukinumab comprised 824.8 subject-years of exposure from studies M2301 and M2302 in the target population of adult subjects with moderate to severe HS.

In total, 721 subjects received secukinumab in Treatment Period 1 (361 subjects in secukinumab Q2W and 360 subjects in secukinumab Q4W), and 1060 subjects received secukinumab during the Entire Study Period (527 subjects in Any secukinumab Q2W and 533 subjects in Any secukinumab Q4W).

The pooled population up to Week 16 comprised 1084 subjects (secukinumab Q2W (N=361), secukinumab Q4W (N=360) and placebo (N=363)). From Week 16 onwards, all subjects received secukinumab (Any secukinumab Q2W (N=527) or Any secukinumab Q4W (N=533)).

Overall, 93.6% of the randomized subjects completed Week 16 of the studies. Safety data for at least 16 weeks are available for all subjects (who had completed the Week 16 visit) and long term for up to 52 weeks, initially for 59.1% of randomized subjects. The results on the full 52-week dataset were subsequently provided (see below). During the Entire Study Period, duration of exposure was similar across all treatment groups with >56% of subjects in the secukinumab Q2W and Q4W groups exposed to treatment for at least 52 weeks and a median exposure of 365 days. Median exposure for the Any secukinumab Q2W and Q4W groups was also comparable (309 vs. 302 days).

Subsequently, the MAH provided within the response to the 1st RSI the full 52-week dataset separately for the two pivotal studies and eventually within the response to the 2nd RSI the requested full pooled 52-week safety data. Exposure to study treatment is summarized for the pooled Entire Study Period in the updated **Table 30**.

Table 30 Duration of exposure to study treatment – Entire Study Period (Safety set) – updated

Duration of exposure	AIN457 Q2W N=361	AIN457 Q4W N=360	Any AIN457 Q2W N=527	Any AIN457 Q4W N=533	Any AIN457 N=1060
Any exposure, n (%)	**361 (100.0)**	**360 (100.0)**	**527 (100.0)**	**533 (100.0)**	**1060 (100.0)**
≥1 week	360 (99.7)	360 (100.0)	523 (99.2)	532 (99.8)	1055 (99.5)
≥2 weeks	359 (99.4)	360 (100.0)	522 (99.1)	531 (99.6)	1053 (99.3)
≥3 weeks	359 (99.4)	359 (99.7)	521 (98.9)	529 (99.2)	1050 (99.1)
≥4 weeks	358 (99.2)	357 (99.2)	520 (98.7)	525 (98.5)	1045 (98.6)
≥8 weeks	355 (98.3)	356 (98.9)	511 (97.0)	519 (97.4)	1030 (97.2)
≥12 weeks	353 (97.8)	350 (97.2)	503 (95.4)	505 (94.7)	1008 (95.1)
≥16 weeks	351 (97.2)	345 (95.8)	494 (93.7)	487 (91.4)	981 (92.5)

Duration of exposure	AIN457 Q2W N=361	AIN457 Q4W N=360	Any AIN457 Q2W N=527	Any AIN457 Q4W N=533	Any AIN457 N=1060
≥24 weeks	320 (88.6)	312 (86.7)	448 (85.0)	440 (82.6)	888 (83.8)
≥32 weeks	292 (80.9)	283 (78.6)	403 (76.5)	397 (74.5)	800 (75.5)
≥40 weeks	262 (72.6)	260 (72.2)	286 (54.3)	290 (54.4)	576 (54.3)
≥52 weeks	205 (56.8)	202 (56.1)	205 (38.9)	202 (37.9)	407 (38.4)
Days					
n	361	360	527	533	1060
Mean	317.3	313.5	286.7	281.7	284.2
SD	95.33	98.60	101.00	104.58	102.79
Median	365.0	365.0	309.0	302.0	306.5
Min - Max	1 - 450	16 - 464	1 - 450	5 - 464	1 - 464
Subject-time (subject-years)	313.6	309.0	413.7	411.1	824.8

Duration of exposure to study treatment is defined as min (date of the last study visit, last dose date + 84 days) minus start date of study treatment + 1. Subject-time in subject-years is calculated as a sum of individual subject duration in days divided by 365.25. For placebo-AIN457 switchers, exposure after the first intake of AIN457 is considered into any AIN457 groups. Source: [AIN457M SCS-Table 1-6].

The treatment groups were 1) secukinumab Q2W, 2) secukinumab Q4W, 3) Any secukinumab Q2W (combination of secukinumab Q2W and placebo-switchers to secukinumab Q2W), 4) Any secukinumab Q4W (combination of secukinumab Q4W and placebo-switchers to secukinumab Q4W) and 5) Any secukinumab (all subjects who received at least one dose of secukinumab).

Full 52-week safety data

During the Entire Study Period, the median duration of exposure was 364 days in the Any secukinumab treatment group in both studies. At the time of final database lock, 72.9% of subjects in secukinumab Q2W group and 77.2% of subjects in secukinumab Q4W group in study M2301, and 78.3% of subjects in secukinumab Q2W group and 68.9% of subjects in secukinumab Q4W group in study M2302, had received treatment with secukinumab for ≥ 52 weeks with a cumulative secukinumab exposure of 456.2 and 450.8 subject-years in study M2301 and M2302, respectively. The cumulative exposure was also comparable between the Any secukinumab Q2W and the Any secukinumab Q4W groups.

Pooled data

Exposure to study treatment was summarized for the pooled 52-week data from both pivotal studies. In total, 1060 adult subjects with moderate to severe HS received secukinumab during the Entire Study Period (527 subjects in Any secukinumab Q2W and 533 subjects in Any secukinumab Q4W), with the overall exposure being 907.0 subject-years in studies M2301 and M2302.

The duration of exposure for both secukinumab treatment groups was comparable in the Entire Study Period.

At Week 16, subjects who were initially randomized to either of the two secukinumab regimens continued on the same dose regimen, and subjects initially randomized to Placebo were randomized to either secukinumab Q2W or Q4W, following a blinded loading dose regimen. Therefore, both the 'Any secukinumab Q2W' and 'Any secukinumab Q4W' groups also included placebo-switchers assigned to these regimens, and the treatment group 'Any secukinumab' included all subjects who took at least one dose of secukinumab.

In the Entire Study Period, the median duration of exposure was 364.0 days for the Any secukinumab treatment group, with a cumulative exposure of 907.0 subject-years. For subjects who switched from placebo to secukinumab at Week 16, exposure only after the first dose of secukinumab is counted.

Cumulative exposure (subject-years) was similar between the secukinumab Q2W (340.2) and Q4W (336.5) groups and similar between the Any secukinumab Q2W group (454.0) and Any secukinumab Q4W group (453.0).
Although disease history and baseline characteristics were generally balanced across the treatment groups (see efficacy section for details), the secukinumab Q2W group comprised a more severe population (more subjects with Hurley stage III, higher lesion count, older age, more smokers, and more subjects rated 'Very severe' on the HS-PGA) compared to the secukinumab Q4W and placebo groups. In addition, consistent with the higher prevalence of subjects in Hurley III, a higher proportion of subjects in the secukinumab Q2W group underwent non-drug therapies and procedures (e.g., abscess excision or drainage) compared to the other treatment groups. Despite these differences between treatment groups, the demographics of the overall population were, according to the MAH, consistent with the population of subjects who completed the Week 52 visit up to the data cut-off date for each study.

Study A2324 (moderate to severe psoriasis): As the Q2W administration of secukinumab 300 mg has recently been approved for use in PsO patients in the EU, a comparison of available safety data from study A2324 was performed to present findings from PsO alongside HS and provide additional long-term safety information for the secukinumab Q2W dose regimen.

Based on the large secukinumab safety database across all indications studied, consisting of data from 20,961 subjects and healthy volunteers in clinical studies, and 680,470 subject-years with post-marketing exposure, the cumulative exposure to secukinumab consists of 34,907.50 subject-years [AIN457 PSUR 26-Dec-2019 to 25-Dec-2020].

Based on experience with the approved dose in PsO (300 mg Q4W) and expected serum concentrations, two secukinumab dosing regimens were evaluated in Studies M2301 and M2302. For both dosing regimens, secukinumab 300 mg was administered subcutaneously at Weeks 0, 1, 2, 3 and 4 as loading injections, followed by maintenance injections on a Q2W or Q4W basis, up to Week 52 as per protocol schedule. No specific dose selection studies for secukinumab were conducted in patients with HS.

Adverse events

Safety results are presented for two separate time periods: the initial placebo-controlled period up to Week 16 (Treatment Period 1) and the Entire Study Period (up to the data cut-off dates for Studies M2301 and M2302) up to Week 52. A direct safety comparison (crude incidences) between secukinumab and placebo can be evaluated up to Week 16. Comparisons of safety reported during the Entire Study Period focus on EAIRs (expressed as incidence rates per 100 subject-years of exposure) due to the relative higher exposure to secukinumab compared to placebo (placebo subjects switched to secukinumab Q2W or Q4W after Week 16). However, treatment comparison of secukinumab to placebo for the Entire Study Period must be interpreted with caution due to the different durations of exposure and given that the AE rate may not be constant over time.

Most frequently occurring adverse events

Treatment Period 1

During Treatment Period 1, the overall incidence of AEs was similar between the secukinumab treatment groups (65.1% and 64.4% in the secukinumab Q2W and Q4W groups, respectively) and the placebo group (65.0%). No meaningful differences in AE frequency or clinical relevance were reported between

the secukinumab Q2W and Q4W groups (**Table 31**), with the vast majority of the reported AEs being non-serious (approximately 98%), mild to moderate in severity (approximately 97%), and not requiring drug discontinuation (approximately 99%).

As expected, based on the known safety profile of secukinumab across various indications and from risks related to the indication of HS, the AEs with the highest frequency were reported in the SOC of Infections and infestations, with similar incidences across the secukinumab groups (30.7% vs. 30.6% in the secukinumab Q2W and Q4W groups, respectively) and placebo group (31.7%), with the most commonly reported AEs being headache (10.4%), nasopharyngitis (8.0%) and (worsening of) hidradenitis (5.1%).

Other commonly affected SOCs (≥10% of subjects in any treatment group) were Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Nervous system disorders, General disorders and administration site conditions, and Musculoskeletal and connective tissue disorders, with similar incidences across treatment groups.

Table 31 Most frequent (≥2% in any treatment group) treatment-emergent adverse events, by preferred term - Treatment Period 1 (Safety set)

Preferred term	AIN457 Q2W N=361 n (%)	AIN457 Q4W N=360 n (%)	Any AIN457 N=721 n (%)	Placebo N=363 n (%)
Any preferred term	235 (65.1)	232 (64.4)	467 (64.8)	236 (65.0)
Headache	38 (10.5)	37 (10.3)	75 (10.4)	29 (8.0)
Nasopharyngitis	33 (9.1)	25 (6.9)	58 (8.0)	29 (8.0)
Hidradenitis	21 (5.8)	16 (4.4)	37 (5.1)	38 (10.5)
Diarrhoea	13 (3.6)	20 (5.6)	33 (4.6)	22 (6.1)
Upper respiratory tract infection	14 (3.9)	9 (2.5)	23 (3.2)	11 (3.0)
Fatigue	8 (2.2)	14 (3.9)	22 (3.1)	10 (2.8)
Nausea	9 (2.5)	10 (2.8)	19 (2.6)	11 (3.0)
Urinary tract infection	8 (2.2)	10 (2.8)	18 (2.5)	8 (2.2)
Pyrexia	9 (2.5)	7 (1.9)	16 (2.2)	6 (1.7)
Arthralgia	12 (3.3)	3 (0.8)	15 (2.1)	13 (3.6)
Oropharyngeal pain	9 (2.5)	6 (1.7)	15 (2.1)	4 (1.1)
Pruritus	9 (2.5)	5 (1.4)	14 (1.9)	7 (1.9)
Back pain	3 (0.8)	10 (2.8)	13 (1.8)	12 (3.3)
Cough	4 (1.1)	8 (2.2)	12 (1.7)	4 (1.1)
Pain in extremity	1 (0.3)	2 (0.6)	3 (0.4)	8 (2.2)

Preferred terms are sorted in descending frequency of AEs in the Any AIN457 group. A subject with multiple AEs with the same preferred term is counted only once for that preferred term.
Source: [AIN457M SCS-Table 2-3]

Entire Study Period

Initial interim (approx. 60%) safety dataset

During the Entire Study Period, in long term AEs were consistent with those observed during Treatment Period 1. After adjusting for exposure, the overall incidence of AEs was lower in the Any secukinumab group than the placebo group (285.2 vs. 412.2 per 100 subject-years). The EAIR rate was lower for the secukinumab Q2W group compared to the secukinumab Q4W group (274.3 vs. 296.7 per 100 subject-years) and for the Any secukinumab Q2W group compared to the Any secukinumab Q4W group (266.4 vs. 306.0 per 100 subject-years) (**Table 32**).

The SOC with the highest EAIR in the Any secukinumab group was Infections and infestations, as reported for Treatment Period 1. A higher incidence was reported in the Any secukinumab Q2W group compared to the Any secukinumab Q4W group (92.5 vs. 84.1 per 100 subject-years), with the most reported PT being nasopharyngitis. No differences were observed in the EAIRs of other SOCs between the secukinumab dose regimens.

The most commonly reported (≥10 per 100 subject-years) AEs by PT in the Any secukinumab group were headache (20.9 per 100 subject-years), (worsening of) hidradenitis and nasopharyngitis (both 14.8 per 100 subject-years). No meaningful differences in AE frequency or clinical relevance were reported between the secukinumab Q2W and Q4W groups, with the majority (approximately 98%) of the reported AEs being non-serious, mild to moderate in severity (approximately 97%) not requiring drug discontinuation (approximately 99%).

Full 52-week safety dataset

There were no new treatment-emergent safety signals identified during the long-term exposure of secukinumab, with the safety profile over the entire study period being similar to Treatment Period 1. The

overall incidence of AEs for both treatment groups was 83.9% in study M2301 and 80.8% in study M2302.

Consistent with the reported Week 16 data, for the Entire Study Period, the overall EAIR for AEs was lower in the Any secukinumab Q2W group (274.6 per 100 subject-years) compared to the Any secukinumab Q4W group (301.6 per 100 subject-years), with no specific SOCs or PTs driving the difference. 'Infections and infestations' was the most commonly reported SOC with a higher incidence in the Any secukinumab Q2W group (94.0 per 100 subject-years) compared to the Any secukinumab Q4W group (87.9 per 100 subject-years). Most of the individual events in the SOC 'Infections and infestations' (>96%) were non-serious, mild (approximately 70%) or moderate (approximately 28%) in severity and did not lead to treatment discontinuation (only approximately 1% of AEs resulted in permanent treatment withdrawal). As was reported in the Week 16 SCS, the most frequent AEs over the Entire Study Period (>5%) included headache, (worsening of) hidradenitis, nasopharyngitis, diarrhea and upper respiratory tract infection, with similar frequencies between the Any secukinumab Q2W and Q4W groups.

Adverse events by system organ class (SOC) and preferred term (PT)

Study M2301

The Exposure Adjusted Incidence Rate (EAIR) of overall AEs in the Entire Study Period was slightly lower in the Any secukinumab Q2W group (291.8 per 100 subject years (SY)) than in the Any secukinumab Q4W group (325.2 per 100 SY).

'Infections and infestations' was the most commonly reported SOC, with higher incidence in the Any secukinumab Q2W group (97.1 per 100 SY) compared to the Any secukinumab Q4W group (82.0 per 100 SY). Other commonly reported AEs by SOCs in the Any secukinumab group were 'Skin and subcutaneous tissue disorders' (53.9 per 100 SY), 'Gastrointestinal disorders' (33.5 per 100 SY), 'Nervous system disorders' (28.0 per 100 SY), 'General disorders and administration site conditions' (23.7 per 100 SY), 'Investigations' (20.9 per 100 SY), and 'Musculoskeletal and connective tissue disorders' (20.1 per 100 SY), with all SOCs showing generally comparable incidence rates in the Any secukinumab Q2W and Q4W dose groups.

The most commonly reported AEs by PT were headache (19.5 per 100 SY in Any secukinumab Q2W; 23.5 per 100 SY in Any secukinumab Q4W), nasopharyngitis (20 per 100 SY in Any secukinumab Q2W; 13.9% per 100 SY in Any secukinumab Q4W), and (worsening of) hidradenitis (14.7 per 100 SY in Any secukinumab Q2W; 13.9 per 100 SY in Any secukinumab Q4W). The incidence of the AEs of nasopharyngitis and pruritus were numerically higher in the Any secukinumab Q2W group compared to the Any secukinumab Q4W group; the incidence of the AEs of diarrhea, headache, nausea, influenza, and fatigue were numerically higher in the Any secukinumab Q4W group than in the secukinumab Q2W group.

Study M2302

The EAIR of overall AEs in the entire study period was comparable between the Any secukinumab Q2W group (258.6 per 100 SY) and the Any secukinumab Q4W group (280.2 per 100 SY).

'Infections and infestations' was the most commonly reported SOC, with similar incidence between the secukinumab treatment groups [Any secukinumab Q2W group (91.0 per 100 SY) compared to the Any secukinumab Q4W group (94.2 per 100 SY)]. Other commonly reported AEs by SOCs in the Any secukinumab group were 'Skin and subcutaneous tissue disorders' (38.1 per 100 SY), 'Gastrointestinal disorders' (32.4 per 100 SY), 'Nervous system disorders' (26.6 per 100 SY), and 'Musculoskeletal and connective tissue disorders' (20.0 per 100 SY), with all SOCs showing generally comparable incidences between the Any secukinumab Q2W and Any secukinumab Q4W groups.

The most commonly reported AEs in the Any secukinumab group were headache (19.3 per 100 SY in the Any secukinumab Q2W and 18.1 per 100 SY in the Any secukinumab Q4W group), (worsening of)

hidradenitis (13.1 per 100 SY in Any secukinumab Q2W and 14.9 per 100 SY in Any secukinumab Q4W group), and nasopharyngitis (13.3 per 100 SY in Any secukinumab Q2W and 11.9 per 100 SY in Any secukinumab Q4W group). The incidences of other AEs were low and comparable between the Any secukinumab Q2W and Any secukinumab Q4W groups. The incidences of AEs of hypertension, pruritus, influenza and sweat gland infection were numerically higher in the Any secukinumab Q2W group compared to the Any secukinumab Q4W group; the incidences of back pain and upper abdominal pain were numerically higher in the Any secukinumab Q4W group than the secukinumab Q2W group.

Exposure-adjusted incidence rate of most frequent (≥2% in any treatment group) treatment-emergent adverse events, by preferred term, for the Entire study period (Safety set) are presented in **Table 32**.

Table 32 Exposure-adjusted incidence rate of most frequent (≥2% in any treatment group) treatment-emergent adverse events, by preferred term - Entire study period Safety set

Preferred term	AIN457 Q2W N=361 n/EX (IR)	AIN457 Q4W N=360 n/EX (IR)	Any AIN457 Q2W N=527 n/EX (IR)	Any AIN457 Q4W N=533 n/EX (IR)	Any AIN457 N=1060 n/EX (IR)	Placebo N=363 n/EX (IR)
- Any preferred term	301/1.08 (278.4)	307/1.04 (295.6)	429/1.56 (274.6)	444/1.47 (301.6)	873/3.03 (287.7)	237/0.57 (414.3)
Headache	64/2.94 (21.7)	59/2.94 (20.1)	78/4.02 (19.4)	83/3.99 (20.8)	161/8.01 (20.1)	30/1.05 (28.7)
Nasopharyngitis	53/3.05 (17.4)	42/3.08 (13.6)	68/4.11 (16.6)	54/4.20 (12.9)	122/8.30 (14.7)	29/1.06 (27.4)
Hidradenitis	41/3.17 (12.9)	43/3.15 (13.7)	59/4.24 (13.9)	61/4.23 (14.4)	120/8.47 (14.2)	38/1.04 (36.5)
Diarrhoea	24/3.24 (7.4)	30/3.14 (9.6)	31/4.36 (7.1)	43/4.25 (10.1)	74/8.61 (8.6)	22/1.06 (20.7)
Upper respiratory tract infection	22/3.25 (6.8)	21/3.24 (6.5)	28/4.36 (6.4)	28/4.37 (6.4)	56/8.73 (6.4)	11/1.09 (10.1)
Pyrexia	22/3.27 (6.7)	16/3.29 (4.9)	27/4.38 (6.2)	25/4.42 (5.7)	52/8.80 (5.9)	6/1.10 (5.5)
Arthralgia	18/3.29 (5.5)	10/3.32 (3.0)	25/4.40 (5.7)	18/4.46 (4.0)	43/8.86 (4.9)	13/1.09 (11.9)
COVID-19	16/3.33 (4.8)	10/3.33 (3.0)	20/4.45 (4.5)	22/4.45 (4.9)	42/8.91 (4.7)	3/1.10 (2.7)
Back pain	11/3.34 (3.3)	20/3.25 (6.2)	14/4.47 (3.1)	26/4.38 (5.9)	40/8.85 (4.5)	12/1.09 (11.0)
Urinary tract infection	16/3.31 (4.8)	15/3.28 (4.6)	18/4.44 (4.1)	22/4.42 (5.0)	40/8.85 (4.5)	8/1.10 (7.3)
Pruritus	19/3.28 (5.8)	9/3.30 (2.7)	26/4.38 (5.9)	13/4.46 (2.9)	39/8.84 (4.4)	7/1.09 (6.4)
Nausea	10/3.33 (3.0)	13/3.28 (4.0)	18/4.43 (4.1)	20/4.42 (4.5)	38/8.85 (4.3)	11/1.09 (10.1)

Preferred term	AIN457 Q2W N=361 n/EX (IR)	AIN457 Q4W N=360 n/EX (IR)	Any AIN457 Q2W N=527 n/EX (IR)	Any AIN457 Q4W N=533 n/EX (IR)	Any AIN457 N=1060 n/EX (IR)	Placebo N=363 n/EX (IR)
Fatigue	10/3.32 (3.0)	17/3.25 (5.2)	15/4.43 (3.4)	21/4.39 (4.8)	36/8.82 (4.1)	10/1.09 (9.2)
Eczema	18/3.32 (5.4)	12/3.30 (3.6)	20/4.45 (4.5)	16/4.45 (3.6)	36/8.90 (4.0)	2/1.11 (1.8)
Oropharyngeal pain	17/3.30 (5.2)	13/3.27 (4.0)	19/4.42 (4.3)	16/4.42 (3.6)	35/8.84 (4.0)	4/1.10 (3.6)
Abdominal pain	11/3.36 (3.3)	13/3.28 (4.0)	13/4.49 (2.9)	21/4.41 (4.8)	34/8.90 (3.8)	3/1.10 (2.7)
Hypertension	17/3.32 (5.1)	10/3.31 (3.0)	22/4.42 (5.0)	12/4.46 (2.7)	34/8.89 (3.8)	4/1.10 (3.6)
Intertrigo	14/3.33 (4.2)	12/3.31 (3.6)	17/4.45 (3.8)	16/4.45 (3.6)	33/8.90 (3.7)	2/1.11 (1.8)
Cough	9/3.35 (2.7)	15/3.26 (4.6)	13/4.47 (2.9)	19/4.41 (4.3)	32/8.88 (3.6)	4/1.10 (3.6)
Lipase increased	11/3.33 (3.3)	14/3.28 (4.3)	13/4.45 (2.9)	16/4.44 (3.6)	29/8.89 (3.3)	3/1.10 (2.7)
Pharyngitis	10/3.33 (3.0)	11/3.30 (3.3)	12/4.45 (2.7)	16/4.44 (3.6)	28/8.89 (3.1)	4/1.11 (3.6)
Toothache	13/3.33 (3.9)	11/3.30 (3.3)	16/4.45 (3.6)	12/4.46 (2.7)	28/8.91 (3.1)	4/1.10 (3.6)
Abdominal pain upper	7/3.36 (2.1)	14/3.27 (4.3)	8/4.50 (1.8)	19/4.42 (4.3)	27/8.91 (3.0)	2/1.11 (1.8)
Dizziness	10/3.33 (3.0)	10/3.28 (3.0)	13/4.46 (2.9)	13/4.43 (2.9)	26/8.89 (2.9)	6/1.10 (5.5)
Bronchitis	10/3.35 (3.0)	11/3.32 (3.3)	10/4.49 (2.2)	15/4.46 (3.4)	25/8.95 (2.8)	5/1.10 (4.5)
Cellulitis	8/3.36 (2.4)	7/3.32 (2.1)	11/4.48 (2.5)	12/4.46 (2.7)	23/8.95 (2.6)	5/1.10 (4.6)
Folliculitis	13/3.33 (3.9)	6/3.33 (1.8)	15/4.46 (3.4)	8/4.49 (1.8)	23/8.95 (2.6)	5/1.10 (4.5)
Psoriasis	12/3.34 (3.6)	9/3.32 (2.7)	12/4.48 (2.7)	11/4.48 (2.5)	23/8.95 (2.6)	1/1.11 (0.9)
Vomiting	7/3.35 (2.1)	8/3.32 (2.4)	12/4.48 (2.7)	11/4.48 (2.5)	23/8.95 (2.6)	1/1.11 (0.9)
Conjunctivitis	9/3.36 (2.7)	10/3.31 (3.0)	9/4.50 (2.0)	13/4.46 (2.9)	22/8.96 (2.5)	1/1.11 (0.9)
Depression	10/3.36 (3.0)	7/3.33 (2.1)	12/4.49 (2.7)	8/4.49 (1.8)	20/8.98 (2.2)	6/1.10 (5.4)

Preferred term	AIN457 Q2W N=361 n/EX (IR)	AIN457 Q4W N=360 n/EX (IR)	Any AIN457 Q2W N=527 n/EX (IR)	Any AIN457 Q4W N=533 n/EX (IR)	Any AIN457 N=1060 n/EX (IR)	Placebo N=363 n/EX (IR)
SARS-CoV-2 test negative	8/3.36 (2.4)	7/3.33 (2.1)	10/4.49 (2.2)	10/4.48 (2.2)	20/8.97 (2.2)	4/1.10 (3.6)
Tonsillitis	8/3.35 (2.4)	6/3.31 (1.8)	11/4.48 (2.5)	9/4.46 (2.0)	20/8.94 (2.2)	1/1.11 (0.9)
Gastroenteritis	9/3.34 (2.7)	7/3.33 (2.1)	10/4.47 (2.2)	9/4.48 (2.0)	19/8.95 (2.1)	2/1.11 (1.8)
Sinusitis	7/3.36 (2.1)	5/3.34 (1.5)	14/4.48 (3.1)	5/4.51 (1.1)	19/8.99 (2.1)	5/1.10 (4.5)
Ligament sprain	7/3.36 (2.1)	8/3.32 (2.4)	9/4.49 (2.0)	9/4.47 (2.0)	18/8.96 (2.0)	0/1.11 (0.0)
SARS-CoV-2 test positive	5/3.39 (1.5)	8/3.33 (2.4)	9/4.51 (2.0)	9/4.49 (2.0)	18/9.00 (2.0)	3/1.10 (2.7)
Skin candida	8/3.37 (2.4)	5/3.34 (1.5)	11/4.50 (2.4)	7/4.49 (1.6)	18/9.00 (2.0)	4/1.10 (3.6)
Suspected COVID-19	8/3.36 (2.4)	4/3.35 (1.2)	9/4.49 (2.0)	9/4.50 (2.0)	18/8.99 (2.0)	1/1.11 (0.9)
Dermatitis	6/3.37 (1.8)	8/3.32 (2.4)	8/4.49 (1.8)	9/4.49 (2.0)	17/8.98 (1.9)	2/1.11 (1.8)
Dermatitis contact	6/3.37 (1.8)	9/3.32 (2.7)	8/4.49 (1.8)	9/4.49 (2.0)	17/8.98 (1.9)	1/1.11 (0.9)
Oral candidiasis	8/3.36 (2.4)	4/3.35 (1.2)	9/4.50 (2.0)	6/4.50 (1.3)	15/9.00 (1.7)	0/1.11 (0.0)
Pain in extremity	5/3.37 (1.5)	5/3.34 (1.5)	8/4.49 (1.8)	7/4.50 (1.6)	15/9.00 (1.7)	8/1.10 (7.3)
Rhinorrhoea	9/3.36 (2.7)	2/3.35 (0.6)	10/4.49 (2.2)	4/4.50 (0.9)	14/8.99 (1.6)	4/1.11 (3.6)

- A subject with multiple adverse events within a primary system organ class is counted only once in the system organ class.
- EX = Exposure per 100 subject-years. IR = Incidence rate per 100 subject-years. For subjects with multiple events within the preferred term, exposure time is censored at time of first event.
- Primary system organ classes are sorted in descending order of frequency in Any AIN457 group.

Severity of adverse events

Adverse events for both the first 16 weeks (Treatment Period 1) and over the Entire Study Period were mostly mild or moderate in severity, with severe events occurring at low frequency (<7%). No imbalance was seen in the severity of AEs between the secukinumab and the placebo groups in Treatment Period 1. The incidence of severe AEs was similar between the Any secukinumab Q2W and Any secukinumab Q4W groups in the Entire Study Period. There was no clustering or pattern of events which would suggest any increased risk of severe events in the secukinumab dose groups over the Entire Study Period.

Treatment Period 1

The majority of AEs reported during Treatment Period 1 were mild (occurring in 40.7% of subjects in secukinumab Q2W, 42.8% in secukinumab Q4W and 36.4% of subjects in placebo) or moderate (21.6% in secukinumab Q2W, 19.2% in secukinumab Q4W and 23.4% in placebo group) in severity. During Treatment Period 1, severe AEs were reported with a similar incidence in the secukinumab Q2W and Q4W groups (2.8% vs. 2.5%) and a slightly higher incidence in the placebo group (5.2%).

By PT, no severe events were reported in more than one subject in any treatment group, with the exception of fatigue (3 subjects in the placebo group) and (worsening of) hidradenitis (2 subjects in the secukinumab Q4W group and 5 subjects in the placebo group).

Entire Study Period

Initial interim (approx. 60%) safety dataset

Most treatment-emergent AEs during the Entire Study Period in the secukinumab groups were mild (37.0% in Any secukinumab Q2W, 40.5% in Any secukinumab Q4W, 38.8% in Any secukinumab) or moderate (33.6% of subjects in Any secukinumab Q2W, 31.9% in Any secukinumab Q4W, 32.7% in Any secukinumab) in severity. Severe events were of low frequency in all groups (<7%). The incidence of severe AEs was similar between the Any secukinumab Q2W and Any secukinumab Q4W groups (6.3% and 6.8%, respectively). The most frequent severe AEs reported for both the secukinumab groups were in the SOC for Infections and infestations (2.5% in Any secukinumab Q2W and 1.9% in Any Q4W). Additional severe events were reported at low frequencies from the Treatment Period 1. There was no clustering or pattern of events which would suggest any increased risk of severe events in the secukinumab groups over the Entire Study Period. All severe AEs (PTs) were in ≤3 subjects except for (worsening of) hidradenitis reported in 4 subjects in Any secukinumab Q2W and in 6 subjects in Any secukinumab Q4W. No specific trends were observed for any of the severe AEs.

Full 52-week safety dataset

Adverse events during both Treatment Period 1 and the Entire Study Period were mostly mild or moderate in severity, with no imbalance seen in the severity of AEs between the secukinumab and the placebo groups. The proportion of subjects with mild AEs during the Entire Study Period in the secukinumab groups were 38.5% in Any secukinumab Q2W and 41.7% in Any secukinumab Q4W, and those with moderate AEs were 35.9% in Any secukinumab Q2W and 34.7% in Any secukinumab Q4W groups. Severe events were reported with similar incidence in the Any secukinumab Q2W and Any secukinumab Q4W groups (7% and 6.9%, respectively). The most frequent severe AEs reported for both the secukinumab groups were in the SOC 'Infections and infestations' (2.7% in Any secukinumab Q2W and 2.1% in Any secukinumab Q4W). All severe AEs (PTs) were in ≤3 subjects, with the exceptions of the following:

- (Worsening of) Hidradenitis (4 subjects in Any secukinumab Q2W and 7 subjects in Any secukinumab Q4W): considered not related to study treatment (except in one subject), transient and resolved with or without treatment (except 3 subjects), not leading to study treatment discontinuation. Three cases occurred before starting study treatment.
- Headache (3 subjects in Any secukinumab Q2W and 1 subject in Any secukinumab Q4W): considered related in one case, transient and resolved with or without treatment. All subjects completed the study with no treatment interruption.
- Sweat gland infection (4 subjects in Any secukinumab Q2W and 1 subject in Any secukinumab Q4W): associated with worsening of HS lesions, considered related in one case, all resolved. All subjects completed the study, with 1 subject interrupting and 1 subject discontinuing the study treatment

Potential relationship of adverse events to study treatment

Treatment Period 1

Adverse events that were suspected to be related to study drug were reported at similar frequencies in the secukinumab groups compared to placebo up in Treatment Period 1 (19.8% in Any secukinumab, 22.0% in placebo). There was no meaningful difference in AEs related to study drug between the secukinumab dose regimens (18.6% in secukinumab Q2W and 21.1% in secukinumab Q4W).

Most of the AEs related to study treatment (≥ 1% in secukinumab groups) were events such as fatigue (1.7% in secukinumab Q2W, 3.1% in secukinumab Q4W and 1.4% in placebo), diarrhea (1.7% in secukinumab Q2W, 1.1% in secukinumab Q4W and 3.6% in placebo), headache (1.4% in secukinumab Q2W, 1.4% in secukinumab Q4W and 0.6% in placebo), upper respiratory tract infections (1.1% in secukinumab Q2W, 0.8% in secukinumab Q4W and 0.6% in placebo), (worsening of) hidradenitis (1.1% in secukinumab Q2W, 0.3% in secukinumab Q4W and 1.4% in placebo) and asthenia (1.1% in secukinumab Q2W, 0.3% in secukinumab Q4W and 0.6% in placebo). All of these AEs suspected to be related to study drug were non-serious, mild to moderate, and did not lead to study discontinuation except for one case of headache in secukinumab Q2W which was considered severe but did not lead to treatment discontinuation, and one case of (worsening of) hidradenitis in placebo suspected to be related to study treatment was considered serious and did not led to discontinuation of study treatment.

Entire Study Period

No clinically meaningful differences were observed in the incidence of treatment-related AEs between the Any secukinumab Q2W and Any secukinumab Q4W groups. Adverse events that were suspected to be related to study drug were reported at similar frequencies in the secukinumab groups compared to placebo in Treatment Period 1 and between the two secukinumab dose groups in the Entire Study Period. No clinically meaningful differences were observed in the incidence of treatment-related AEs between the Any secukinumab Q2W and Any secukinumab Q4W groups. In addition, the types of treatment-related AEs reported during the Entire Study Period were consistent with those reported in Treatment Period 1.

Adverse drug reactions update

In order to update the current list of ADRs for secukinumab, data pooling was performed from secukinumab studies in multiple indications including HS, PsO, PsA, AS and nr-axSpA. The following sources and cut-off dates obtained from previous submission packages (placebo-controlled period) were utilized for the creation of the updated ADR table:

- HS [Study M2301] and [Study M2302] – up to Week 16
- PsO [Study CAIN457A2302], [Study CAIN457A2303], [Study CAIN457A2308] and [Study CAIN457A2309] – up to Week 12
- PsA [Study CAIN457F2306] and [Study CAIN457F2312] – up to Week 16
- AS [Study CAIN457F2305] and [Study CAIN457F2310] – up to Week 16
- nr-axSpA [Study CAIN457H2315] – up to Week 16

The following ADRs were identified and classified based on their frequency category:

- Very common: Upper respiratory tract infection (HLT)
- Common: Fatigue, diarrhea, headache, oral herpes, nausea, rhinorrhea
- Uncommon: Oral candidiasis, IBD, otitis externa, conjunctivitis, lower respiratory tract infection, neutropenia, tenia pedis, dyshidrotic eczema and urticaria. Note: For ADR 'tinea pedis' the frequency

category changed from previously identified category 'common' to 'uncommon' because of MedDRA version update.

- Rare: Anaphylactic reactions

Of note, there were no cases of anaphylactic reaction during the conduct of the studies.

Since there is no case of hypersensitivity vasculitis or exfoliative dermatitis within the pool of data used to update the ADR table, the currently approved frequency category of both terms (as per procedure IAIN-0081 for hypersensitivity vasculitis and procedure IAIN-0054 for exfoliative dermatitis) is kept.

Comparison of adverse events between HS studies and Study A2324

The overall safety profile of the secukinumab Q2W dose regimen in HS (pooled data from Studies M2301 and M2302) was comparable to that of moderate to severe PsO (Study A2324). While the overall EAIR of treatment-emergent AEs was higher in HS than in PsO subjects (HS studies: 266.4 in Any secukinumab Q2W and 306.0 in Any secukinumab Q4W; Study A2324: 176.1 in Any secukinumab Q2W and 180.2 in Any secukinumab Q4W), it is important to note that there was no difference in the incidence of AEs between the secukinumab Q2W and Q4W regimens within each indication.

The higher EAIRs (per 100 subject-years) of AEs in HS was primarily driven by differences in the Infections and infestations SOC (HS studies: 92.5 in Any secukinumab Q2W, 84.1 in Any secukinumab Q4W; Study A2324: 62.2 in Any secukinumab Q2W, 71.5 in Any secukinumab Q4W), with the difference largely driven by nasopharyngitis. Notably, the HS development program was conducted in the midst of the COVID-19 pandemic, which was announced when approximately 80% of the population was enrolled. The differences between HS and PsO are also likely linked to disease-specific aspects (i.e., HS population presenting with a higher inflammatory burden and broad spectrum of associated comorbidities, as well as open wounds) and highlighted by the higher EAIRs of PTs often reported as associated with HS (i.e., headache, (worsening of) hidradenitis and diarrhoea) (Reddy et al 2019, Ring et al 2017).

Serious adverse event/deaths/other significant events

Deaths

Treatment Period 1

No deaths were reported in Treatment Period 1 in either study. Non-fatal SAEs and discontinuations were infrequent and occurred at comparable rates between the secukinumab and placebo groups (**Table 33**).

Table 33 Deaths, other serious or clinically significant adverse events or related discontinuations - Treatment Period 1 (Safety set)

	AIN457 Q2W N = 361 n (%)	AIN457 Q4W N = 360 n (%)	Any AIN457 N = 721 n (%)	Placebo N = 363 n (%)
Subjects with any AE(s)	235 (65.1)	232 (64.4)	467 (64.8)	236 (65.0)
Subjects with serious or other significant events				
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAE(s)	9 (2.5)	9 (2.5)	18 (2.5)	11 (3.0)
Discontinued study treatment due to any AE(s)	6 (1.7)	5 (1.4)	11 (1.5)	5 (1.4)

Source: [SCS Appendix 1-Table 3.5-1.1]

Entire Study Period

Two deaths (one subject in secukinumab Q4W and one subject in Any secukinumab Q4W) were reported after Treatment Period 1 for the studies. Neither death was suspected to be related to the study treatment (**Table 34**).

Table 34 Overview of deaths (Entire Study Period)

Treatment received	Primary preferred term, (Event contributing to death)	Study day relative to start date of study medication / Number of days since last dose of study medication	Causality (per investi-gator)	Comment/ assessment
AIN457 Q4W	Myocardial infarction	219/21	No	Subject with pre-existing aortic valve stenosis who experienced myocardial infarction and died on Day 219, 21 days after the last (18^{th}) study treatment administration (Vist Week 28).
Any AIN457 Q4W	Gastrointestinal haemorrhage	249/79	No	Subject with pre-existing Crohn's disease who had urinary tract infection from Day 1 discontinued study treatment on Day 170 due to nummular eczema. On Day 219 (49 days after last study treatment) the patient presented with an acute upper gastrointestinal hemorrhage (severe, serious). The subject was hospitalized and died due to upper gastrointestinal hemorrhage due to multiple duodenal ulcers on Day 249, 79 days after last study treatment administration (Placebo in Treatment Period 1 and secukinumab Q4W in Treatment Period 2).

Source: [Study M2302-Listing 14.3.2-1, Listing 16.2.7-1, Section 14.3.3]

Non-fatal SAEs and treatment discontinuations due to AEs occurred at comparable rates between the treatment groups (

Table 35 for study M2301 and **Table 36** for study M2302).

Study M2301

No deaths were reported during the entire treatment duration.

After the Week 16 primary analysis cut-off date (01-Oct-2021), non-fatal SAEs were reported in 3 new subjects (5 new SAEs), while there were no additional patients with AEs leading to discontinuation of study treatment (more details are presented in the serious adverse events section below).

Overall, the incidence of non-fatal SAEs was similar between the Any secukinumab Q2W (18 subjects, 6.8%) and Q4W (19 subjects, 7.1%) groups. The incidence of AEs leading to discontinuation of study treatment was also similar in the Any secukinumab Q2W (11 subjects, 4.1%) and Q4W (7 subjects, 2.6%) groups (

Table 35).

Table 35 Study M2301: Deaths, other serious or clinically significant adverse events or related discontinuations - Entire study period (Safety set)

	AIN457 Q2W N=181 n (%)	AIN457 Q4W N=180 n (%)	Any AIN457 Q2W N=266 n (%)	Any AIN457 Q4W N=267 n (%)	Any AIN457 N=533 n (%)
Subjects with any AE(s)	154 (85.1)	154 (85.6)	220 (82.7)	227 (85.0)	447 (83.9)
Subjects with serious or other significant events					
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAE(s)	13 (7.2)	9 (5.0)	18 (6.8)	19 (7.1)	37 (6.9)
Discontinued study treatment due to any	10 (5.5)	5 (2.8)	11 (4.1)	7 (2.6)	18 (3.4)

Source: [Appendix 2 Study M2301 Table 14.3.1-6.2]

Study M2302

No new deaths or new subjects with AEs leading to discontinuation of study treatment were reported since the primary analysis cut-off date (23-Sep-2021). Five additional subjects reported non-fatal SAEs since the primary analysis cut-off date (more details are presented in the serious adverse events section below).

Overall, the incidence of non-fatal SAEs and AEs leading to discontinuation was similar between the Any secukinumab Q2W and Any secukinumab Q4W groups. Non-fatal SAEs were reported in 22 (8.4%) subjects in the Any secukinumab Q2W group and 21 (7.9%) subjects in the Any secukinumab Q4W group. Nine (3.4%) subjects in the Any secukinumab Q2W group discontinued the study treatment due to any AEs, compared to 10 (3.8%) subjects in the Any secukinumab Q4W group (**Table 36**).

Table 36 Study M2302: Deaths, other serious or clinically significant adverse events or related discontinuations - Entire study period (Safety set)

	AIN457 Q2W N=180 n (%)	AIN457 Q4W N=180 n (%)	Any AIN457 Q2W N=261 n (%)	Any AIN457 Q4W N=266 n (%)	Any AIN457 N=527 n (%)
Subjects with any AE(s)	147 (81.7)	153 (85.0)	209 (80.1)	217 (81.6)	426 (80.8)
Subjects with serious or other significant events					
Death	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.8)	2 (0.4)
Non-fatal SAE(s)	19 (10.6)	14 (7.8)	22 (8.4)	21 (7.9)	43 (8.2)
Discontinued study treatment due to any (AEs)	7 (3.9)	9 (5.0)	9 (3.4)	10 (3.8)	19 (3.6)

Source: [Appendix 2 Study M2302 Table 14.3.1-6.2]

Table 37 Deaths, other serious or clinically significant adverse events or related discontinuations - Entire Study Period (Safety set)

	AIN457 Q2W N=361 n (%)	AIN457 Q4W N=360 n (%)	Any AIN457 Q2W N=527 n (%)	Any AIN457 Q4W N=533 n (%)	Any AIN457 N=1060 n (%)
Subjects with any AE(s)	301 (83.4)	307 (85.3)	429 (81.4)	444 (83.3)	873 (82.4)
Subjects with serious or other significant events					
Death	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.4)	2 (0.2)
Non-fatal SAE(s)	32 (8.9)	23 (6.4)	40 (7.6)	40 (7.5)	80 (7.5)
Discontinued study treatment due to any AE(s)	17 (4.7)	14 (3.9)	20 (3.8)	17 (3.2)	37 (3.5)

Source: [Appendix 2 - Table 3.5-2.1]

Serious adverse events

Treatment Period 1

In Treatment Period 1, the incidence of SAEs was low and comparable for both secukinumab regimens and placebo (2.5% for both secukinumab Q2W and secukinumab Q4W versus 3.0% for placebo) with no pattern in the type of event reported. The most commonly reported SAEs for secukinumab in Treatment Period 1 were in the SOC Infections and infestations (**Table 38**).

SAEs in the SOC of Infections and infestations occurred at a similar frequency in the placebo group and the Any secukinumab group (5 subjects (0.7%, 1 in secukinumab Q2W and 4 in secukinumab Q4W) in Any secukinumab versus 3 subjects (0.8%) in placebo). SAEs in the SOCs of Cardiac disorders, Hepatobiliary disorders, Immune system disorders, Musculoskeletal and connective disorders and Psychiatric disorders were reported only in the secukinumab groups, with low rates of ≤0.3%, involving 1-2 subjects, in both secukinumab groups.

All reported SAEs were in single subjects with the exception of (worsening of) hidradenitis SAEs, which were reported in 2 subjects in the secukinumab Q2W and in 2 subjects in placebo group. There were no serious cases of (worsening of) hidradenitis in the secukinumab Q4W group. All cases of (worsening of) hidradenitis which were serious were of moderate severity and did not lead to study treatment discontinuation. During Treatment Period 1, 5 SAEs were suspected to be related to study treatment. These included PTs of suicide attempt, urinary tract infection, colitis ulcerative (one subject each in secukinumab Q2W), inflammatory bowel disease (one subject in secukinumab Q4W) and hidradenitis (one subject in placebo).

Table 38 Treatment-emergent serious adverse events, by preferred term - Treatment Period 1 (Safety set)

Preferred term	AIN457 Q2W N=361 n (%)	AIN457 Q4W N=360 n (%)	Any AIN457 N=721 n (%)	Placebo N=363 n (%)
Any preferred term	9 (2.5)	9 (2.5)	18 (2.5)	11 (3.0)
Hidradenitis	2 (0.6)	0 (0.0)	2 (0.3)	2 (0.6)
Amyloidosis	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Appendicitis	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Arrhythmia	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Basal cell carcinoma	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Cellulitis	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Cholecystitis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)

Preferred term	AIN457 Q2W N=361 n (%)	AIN457 Q4W N=360 n (%)	Any AIN457 N=721 n (%)	Placebo N=363 n (%)
Colitis ulcerative	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Confusional state	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Inflammatory bowel disease	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Inguinal hernia	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Intentional overdose	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Osteoarthritis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Otitis externa	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Pelvi-ureteric obstruction	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Suicide attempt	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Sweat gland infection	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Urinary tract infection	1 (0.3)	0 (0.0)	1 (0.1)	1 (0.3)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
COVID-19 pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Clostridium difficile colitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Diarrhoea haemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Foot fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Glomerular vascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Lung cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ureterolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Preferred terms are sorted in descending frequency of AEs in the Any AIN457 group. A subject with multiple AEs with the same preferred term is counted only once for that preferred term. Source: [SCS Appendix 1-Table 3.2-1.1]

SAEs in Treatment Period 1 for subjects with confirmed or suspected COVID-19 infection

SAEs that occurred in Treatment Period 1 in subjects with confirmed or suspected COVID-19 infection were reported only within the placebo group (n=2), with SAEs of COVID-19 pneumonia and glomerular vascular disorder.

Entire Study Period

The incidence rates of SAEs in the Entire Study Period were low and comparable among the Any secukinumab Q2W and Any secukinumab Q4W treatment groups.

Study M2301

Overall, the incidence of treatment-emergent SAEs during the entire study period was 6.8% in the Any secukinumab Q2W group and 7.1% in the Any secukinumab Q4W group. Most SAEs were reported by one subject each, except for (worsening of) hidradenitis which was reported in 4 (1.5%) subjects in the Any secukinumab Q2W and 4 (1.5%) subjects in Any secukinumab Q4W group, sweat gland infection which was reported in 3 (1.1%) subjects in the Any secukinumab Q4W group compared to 1 (0.4%) subject in the Any secukinumab Q2W group and pneumonia which was reported in 2 (0.7%) subjects in the Any secukinumab Q4W group compared to none in the Any secukinumab Q2W group.

After the Week 16 PEA, 5 SAEs were reported in 3 new subjects (2 subjects in the secukinumab Q2W group, PTs: suicidal ideation, goitre; 1 subject in the placebo Q4W group, PT: peritonsillar abscess). In addition, 2 new SAEs (PTs: hidradenitis, sweat gland infection) were reported in a subject in the secukinumab Q4Wgroup who already experienced a SAEs prior to the PEA cut-off. All these SAEs

resolved, and they were not considered to be causally related to secukinumab.

Study M2302

The incidence of treatment-emergent SAEs during the entire study period was 8.4% in the Any secukinumab Q2W group and 8.6% in the Any secukinumab Q4W group. Most SAEs were reported by one subject each, except for (worsening of) hidradenitis which was reported in 5 (1.9%) subjects in the Any secukinumab Q2W group compared to none in the Any secukinumab Q4W group, and acute kidney injury and pyrexia which were each reported by 2 (0.8%) subjects in the Any secukinumab Q2W group compared to none in the Any secukinumab Q4W group; conversely, intravertebral disc protrusion was reported in 2 subjects (0.8%) in the Any secukinumab Q4W group compared to none in the Any secukinumab Q2W group.

After the Week 16 PEA, 9 SAEs were reported in 5 new subjects (4 subjects in the secukinumab Q2W group, PTs: depression, obsessive compulsive disorder, nephrolithiasis, acute kidney injury, abdominoplasty; 1 subject in the placebo Q4W group, PT: joint dislocation). In addition, 3 new SAEs (PTs: pyrexia, acute kidney injury, hypotension) were reported in a subject in the secukinumab Q2W group who already experienced an SAE prior to the PEA cut-off. All these SAEs were not suspected by the investigator to be related to study treatment.

Pooled data (studies M2301 and M2302)

At Week 16, the incidence rates of SAEs in the Entire Study Period were low and comparable among the Any secukinumab Q2W and Any secukinumab Q4W treatment groups. In addition, the general profile of SAEs during the Entire Study Period was comparable to Treatment Period 1.

In the Entire Study Period, the crude incidence of SAEs were 7.6% in Any secukinumab Q2W, 7.9% in Any secukinumab Q4W. The most commonly reported SAEs for secukinumab during the Entire Study Period were in the SOCs Infections and infestations (3.3% in Any secukinumab) and Skin and subcutaneous tissue disorders (1.2% in Any secukinumab). The rest of the SAEs in the other SOCs showed low rates (≤0.5% in Any secukinumab), involving 1-2 subjects (by PT), in either of the Any secukinumab treatment groups.

All SAEs (PTs) occurred in ≤3 subjects, with the exception of SAEs of (worsening of) hidradenitis and sweat gland infections (PTs), which was reported in 13 and 6 subjects in the Any secukinumab group, respectively. This is expected considering the recurring nature of HS, and the disease severity in these subjects with most having Hurley Stage III disease. During the Entire Study Period, 16 SAEs were suspected to be related to study treatment. These included 9 SAEs in subjects in the Any secukinumab Q2W group (hidradenitis, abscess, large intestine infection, skin candida, sweat gland infection, suicide attempt, urinary tract infection, colitis ulcerative and systemic inflammatory response syndrome), 6 SAEs in subjects in the Any secukinumab Q4W group (inflammatory bowel disease, pneumonia, hidradenitis, influenza, scrotal inflammation, and cellulitis) and one in a subject on placebo (hidradenitis).

No clinically meaningful differences in the EAIRs of total SAEs were observed across the treatment groups (9.4 per 100 subject-years in Any secukinumab and 10.1 per 100 subject-years in placebo) nor between the secukinumab dose regimen groups (9.1 per 100 subject-years in Any secukinumab Q2W and 9.6 per 100 subject-years in Any secukinumab Q4W). Narratives for subjects with SAEs were provided.

Adverse events leading to discontinuation

Interim (approx. 60%) safety dataset

In the Entire Study Period, the incidence of SAEs was low and comparable for both secukinumab groups (6.6% in Any secukinumab Q2W, 7.5% in Any secukinumab Q4W) with no pattern in the type of events reported. The general profile of SAEs over the Entire Study Period was comparable to Treatment Period 1. The most commonly reported SAEs for secukinumab during the Entire Study Period were from the SOC Infections and infestations (3.1% in Any secukinumab), primarily due to Sweat gland infection (0.4%) and Cellulitis (0.3%), and the SOC Skin and subcutaneous tissue disorders (1.1% in Any secukinumab), due to (worsening of) hidradenitis (1.1%). The rest of the SAEs in the other SOCs showed low rates of ≤0.5% (in Any secukinumab), involving 1-2 subjects (by PT), in both Any secukinumab treatment groups. No clinically meaningful differences in the incidence rates of SAEs by SOCs were observed across the Any secukinumab Q2W and Any secukinumab Q4W groups.

No clinically meaningful differences in the EAIRs of total SAEs were observed across the treatment groups (9.4 per 100 subject-years in Any secukinumab and 10.1 per 100 subject-years in placebo) or between the secukinumab dose regimen groups (8.7 per 100 subject-years in Any secukinumab Q2W and 10.1 per 100 subject-years in Any secukinumab Q4W). The EAIRs of SAEs in the SOC Infections and infestations were comparable in the Any secukinumab Q2W and Any secukinumab Q4W groups 2.7 per 100 subject-years in Any secukinumab Q2W versus 5.5 per 100 subject-years in Any secukinumab Q4W).

All SAEs (PTs) were in ≤3 subjects except for the SAEs of (worsening of) hidradenitis, which was reported in 9 subjects in the Any secukinumab Q2W group and in 3 subjects in the Any secukinumab Q4W group. No specific trend was observed for any of the SAEs. During the Entire Study Period, 15 SAEs were suspected to be related to study treatment. In addition to PTs noted in Treatment Period 1, these included 5 SAEs in subjects in the Any secukinumab Q2W group (hidradenitis, abscess, large intestine infection, skin candida and systemic inflammatory response syndrome) and 5 SAEs in subjects in the Any secukinumab Q4W group (pneumonia, hidradenitis, influenza, scrotal inflammation, and cellulitis).

Full 52-week safety dataset

In the Entire Study Period, the incidence of AEs causing discontinuation was comparable between the Any secukinumab Q2W and Q4W groups.

Study M2301

No additional subjects who discontinued study treatment due to AEs were reported since the Week 16 PEA cut-off date (01-Oct-2021).

Overall, the incidence of AEs leading to discontinuation was low and similar in both Any secukinumab Q2W and Q4W groups. In total, 11 subjects (4.1%) in the Any secukinumab Q2W group discontinued study treatment due to AEs compared to 7 subjects (2.6%) in the Any secukinumab Q4W group. All these events were isolated incidences, and each of them were reported in no more than 1 subject. At the final DBL, in 3 subjects (1 each in the secukinumab Q2W (PT: hidradenitis), secukinumab Q4W (PT: hidradenitis), and placebo-Q2W (PT: hematemesis) groups) the action taken with study treatment due to AE was updated compared to the Week 16 PEA from "drug withdrawn" to "dose not changed".

At time of the final DBL, the action taken with the study treatment due to AE (ear infection) was updated from "drug interrupted" to "drug withdrawn" in 1 subject in the secukinumab Q2W group, and one additional AE (PT: impetigo) leading to discontinuation was reported for a subject in the placebo-Q4W group who had already reported treatment discontinuation due to an AE of fungal external otitis (i.e., subject discontinued treatment due to these two AEs).

Study M2302

At the time of the final DBL, no additional subjects who discontinued study treatment due to AEs were reported since the Week 16 PEA cut-off date (23-Sep-2021).

As reported in the Week 16 CSR, the incidence of AEs leading to discontinuation was low and similar in both the Any secukinumab Q2W and the Any secukinumab Q4W groups. At Week 52 final analysis, nine (3.4%) subjects in the Any secukinumab Q2W group discontinued study treatment due to AEs compared to 10 (3.8%) subjects in the Any secukinumab Q4W group. All these events were isolated incidences, each reported in only one subject, and the majority of them were not suspected to be related to study treatment.

Pooled data

In total, 20 (3.8%) subjects in the Any secukinumab Q2W group discontinued study treatment due to AEs compared to 17 (3.2%) subjects in the Any secukinumab Q4W group. Two AEs caused discontinuation in more than one subject: (worsening of) hidradenitis and abdominal pain, both in 1 subject each in the Any secukinumab Q2W and Q4W groups. The events of (worsening of) hidradenitis and abdominal pain were non-serious. Adverse events of (worsening of) hidradenitis were mostly events of recurrence or flares of HS . All other PTs were isolated events with each reported in no more than 1 subject. Narratives for subjects with AEs leading to study treatment discontinuation were provided.

Comparison of serious adverse events between HS studies and study A2324

The EAIRs of SAEs in subjects treated with secukinumab in the Entire Study Period was comparable between the HS population (Studies M2301 and M2302) and the psoriasis population (Study A2324) for Any secukinumab Q2W (8.7 and 8.8 per 100 subject-years, respectively) and was comparable in the psoriasis population for Any secukinumab Q4W (10.1 and 14.0 per 100 subject-years, respectively). All SAEs (PTs) were in $\leq$ 3 subjects except (worsening of) hidradenitis SAE, which was reported in 9 subjects in the Any secukinumab Q2W group and in 3 subjects in the Any secukinumab Q4W group in the two HS studies only.

Safety topics of interest

Safety topics of interest for secukinumab were evaluated up to Week 16 (Treatment Period 1) and for the Entire Study Period, based upon reported treatment-emergent AEs for all treatment groups: compound and class-related risks, important identified risks, important potential risks, and other safety topics of interest. Along with the Standardized MedDRA Queries (SMQ), risks were also identified using customized Company MedDRA Queries (NMQ).

Treatment Period 1

Compound and class-related risks

Compound and class-related risks reported during Treatment Period 1 included various infections (Infectious pneumonia, Fungal infections, Viral herpes, Skin structure infections and Staphylococcal infections) as well as malignancies [Malignant or unspecified tumours (except non-melanoma skin cancer (NMSC), Basal cell carcinoma (BCC) and skin squamous cell carcinoma (SCC)] and Skin tumours (malignant or unspecified).

The most frequently reported compound and class-related risk was Infections of skin structures (NMQ), with a comparable incidence in the two secukinumab groups (13.0% in the secukinumab Q2W group, 14.2% in the secukinumab Q4W group) and a slightly higher incidence in the placebo group (17.6%). The

incidence of Infectious pneumonia (SMQ broad), Herpes viral infections (HLT) and Staphylococcal infections (HLT) was also comparable between the secukinumab Q2W and Q4W groups and placebo.

The incidence of Fungal infectious disorder (HLGT) was slightly higher in the secukinumab Q2W group compared to the secukinumab Q4W and placebo groups (5.3% in secukinumab Q2W, 3.9% in secukinumab Q4W, 2.8% in placebo). The PTs were all muco-cutaneous events. Although there is a small numerical difference between the secukinumab dose regimens and placebo for the incidence of fungal infections, this difference was not clinically important as all cases were non-serious, manageable with standard therapy and of limited duration. There was no pattern observed in terms of latency, the PTs included predominantly vulvovaginal mycotic infections and skin candida. Approximately 21% of subjects affected by Fungal infectious disorder (HLGT) were in Hurley stage III and 81% had previous exposure to systemic antibiotics. All events were mild to moderate and at the time of data cut-off approximately 90% of the events that occurred in Treatment Period 1 were considered resolved and none led to study treatment discontinuation or interruption.

One subject in the secukinumab Q2W group discontinued study treatment due to sinusitis and 1 subject in the placebo group discontinued study treatment due to upper respiratory tract infection.

The incidence of malignant or unspecified tumours (SMQ excl BCC and SCC) (NMQ), non-melanoma skin cancer (BCC and SCC) (NMQ) (broad) and skin tumours malignant and unspecified (NMQ) (broad) was low (5 subjects in the secukinumab Q4W group and 2 subjects in the placebo group). No AEs related to these risks were reported in the secukinumab Q2W group.

Important identified and potential risks

Important identified risks for secukinumab include Infections and Hypersensitivity, the incidence of which were comparable between the secukinumab Q2W and Q4W groups and placebo. The risk of Infections and infestations (SOC) had the highest incidence of all safety topics of interest during Treatment Period 1.

Important potential risks for secukinumab include Malignant or unspecified tumours, MACE, Suicidal ideation and behavior, and Hepatitis B reactivation. Of these important potential risks, only Malignant or unspecified tumors (SMQ) and Suicide/self-injury (SMQ) were reported during Treatment Period 1 (**Table 39**); the incidence of these events was similar between secukinumab and placebo.

Within the Malignant or unspecified tumours (SMQ) category, events included anal cancer stage 0, squamous cell carcinoma in-situ lesions of the vulva and vulval cancer (1 subject in the secukinumab Q4W group), basal cell carcinoma (right clavicle) (1 subject in the secukinumab Q4W group), small papillary urothelial benign tumor (urinary tract neoplasm) (1 subject in the placebo group) and metastatic lung cancer (1 subject in the placebo group).

Table 39 Incidence of important identified and potential risks - Treatment Period 1 (Safety set)

Risk Category **Risk Name** Level 1	**AIN457 Q2W** **N=361** **n (%)**	**AIN457 Q4W** **N=360** **n (%)**	**Any AIN457** **N=721** **n (%)**	**Placebo** **N=363** **n (%)**
Important identified risk				
Hypersensitivity				
Hypersensitivity (SMQ) (narrow)	19 (5.3)	14 (3.9)	33 (4.6)	16 (4.4)
Infections				
Infections and infestations (SOC)	111 (30.7)	111 (30.8)	222 (30.8)	115 (31.7)
Important potential risk				
Malignant or unspecified tumours				
Malignant or unspecified tumours (SMQ)	0 (0.0)	2 (0.6)	2 (0.3)	2 (0.6)

Risk Category Risk Name	AIN457 Q2W N=361	AIN457 Q4W N=360	Any AIN457 N=721	Placebo N=363
Level 1	n (%)	n (%)	n (%)	n (%)
Suicidal ideation and behavior				
Suicide/self-injury (SMQ)	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)

Level 1 within risk name is sorted in descending order of frequency in the Any AIN457 column. A subject with multiple occurrences of a level under one treatment is counted only once for the same risk for that treatment. Source: [AIN457M SCS-Table 2-14]

Other safety topics of interest

Based on the known safety profile of secukinumab, other safety topics of interest included IBD (AEs by PTs of IBD, ulcerative colitis or Crohn's disease), Neutropenia (by CTCAE grade) and Candida infections (HLT) within the identified risk of 'Infections'. Given that Studies M2301 and M2302 were undertaken during the COVID-19 pandemic, COVID-19 infection (suspected and confirmed cases) was also considered a safety topic of interest. The overall incidence of these safety topics of interest was rare and generally balanced across the treatment groups with no treatment-emergent signals identified.

An increased risk of IBD is known to occur in patients with HS. New onset IBD was rare and reported in only 2 subjects during Treatment Period 1. One subject in the secukinumab Q2W treatment group discontinued study treatment due to an SAE of ulcerative colitis and 1 subject in the secukinumab Q4W group discontinued study treatment due to an SAE of IBD. Both cases were considered by the Investigator to be related to study treatment.

Neutropenia was also rare, and mostly grade 1 or 2 events. Grade 3 neutropenia (<1.0 - 0.5 x 10E9/L) was reported in 2 subjects (1 subject in the secukinumab Q2W group and 1 subject in the placebo group). Both subjects had normal baseline values. The subject on placebo experienced grade 3 neutropenia at Week 16; this was a single event and the subject's neutrophil count returned to normal at a subsequent visit. The subject on secukinumab Q2W with grade 3 neutropenia (single event) improved to grade 2 and 1 at the subsequent visits. Both subjects completed treatment and the study. There were no grade 4 neutropenia events.

The incidence of Candida infections (HLT: including PTs of oral candidiasis, skin candida, vulvovaginal candidiasis, candida infection and balanitis candida) was low, with a similar incidence reported across all treatment groups (1.9% in the secukinumab Q2W group and 1.7% in both the secukinumab Q4W and placebo groups). The majority of these cases were non-serious and manageable.

In addition, there were 13 suspected and confirmed cases of COVID-19 reported during Treatment Period 1 (6 cases in the secukinumab Q2W group, 3 in the secukinumab Q4W group and 4 in the placebo group). The majority of these cases of COVID-19 infection were mild, all cases resolved, and none led to study discontinuation.

Entire Study Period

Interim (approx. 60%) safety dataset

Compound and class-related risks

With respect to EAIRs, the most frequently reported compound and class-related risk was Infections of skin structures (NMQ), as observed during Treatment Period 1, known to be a complication of HS. The EAIR of this risk was comparable in the secukinumab Q2W and Q4W groups (40.0 and 40.9 per 100 subject-years) and in Any secukinumab Q2W and Q4W groups (41.6 and 41.8 subject-years). The EAIR of the other risks related to infections was generally comparable between the treatment groups, with the exception of Fungal infectious disorder (HLGT), which was higher in the Any secukinumab Q2W group compared to the Any secukinumab Q4W group (Any secukinumab Q2W: 14.4 per 100 subject-years; Any

secukinumab Q4W: 9.7 per 100 subject-years; placebo: 9.1 per 100 subject-years). Consistent with the AEs reported during Treatment Period 1, the AEs of fungal infection by PT were all muco-cutaneous events, except for 1 case of onychomycosis. The PTs predominantly included skin candida, vulvovaginal mycotic infections, and oral candidiasis. Oesophageal candidiasis (NMQ, narrow) was reported in 1 subject in the Any secukinumab Q4W group; no cases of oesophageal candidiasis were reported in the Any secukinumab Q2W group. Approximately 35% of subjects affected by Fungal infectious disorder (HLGT) were in Hurley stage III and approximately 83% had previous exposure to systemic antibiotics. All events were of mild to moderate severity, except for 3 events that were severe, and, at the time of data cut-off, approximately 82% were considered resolved; only two cases led to study treatment interruption and two cases led to study treatment discontinuation.

The majority of these cases were non-serious and managed with topical anti-fungal agents. In the Any secukinumab Q2W group, there was one serious event of skin candida (worsening of inguinal intertrigo, an event ongoing in Treatment Period 1) in a subject who switched from placebo to Any secukinumab Q2W in Treatment Period 2, the event was considered serious, suspected to be related to study treatment and led to discontinuation of the study treatment.

Three additional subjects discontinued study treatment due to an infection: a serious event of worsening of scrotal infection was reported in 1 subject in the Any secukinumab Q4W group (severe and not suspected to be related to study treatment), vulvovaginal candidiasis in 1 subject in the secukinumab Q4W group (non-serious, severe and suspected to be related to study treatment and large intestinal infection in 1 subject in the secukinumab Q2W group (serious event of infectious colitis, severe and suspected to be related to study treatment).

The EAIRs incidence of Malignant or unspecified tumours (SMQ excl BCC and SCC) (NMQ), Non-melanoma skin cancer (BCC and SCC) (NMQ, broad) and skin tumours malignant and unspecified (NMQ, broad) was low (2 subjects in the secukinumab Q2W group, 5 subjects in the secukinumab Q4W group and 2 subjects in the placebo group).

Important identified and potential risks

As observed during Treatment Period 1, in the Entire Study Period, 'Infections' was also the most frequently reported risk. EAIRs for the Infections and infestations (SOC) were higher in the secukinumab Q2W vs. Q4W groups (92.9 and 85.6 subject-years) and in the Any secukinumab Q2W vs. Q4W groups (94.0 and 84.7 subject-years). EAIRs for Hypersensitivity (SMQ, narrow) were reported at a similar incidence in all treatment groups. No cases of anaphylaxis were reported in either study.

Important potential risks of malignant or unspecified tumours (SMQ), suicide/self-injury (SMQ), and MACE (NMQ) events were each reported in ≤2 subjects in any treatment group during the Entire Study Period, with no imbalance or treatment-emergent signals identified. No events related to the risk of Hepatitis B reactivation were reported.

Events of MACE (NMQ) were reported in 2 subjects (1 in the secukinumab Q4W group and 1 in the Any secukinumab Q4W group). Both cases were considered not related to study treatment and occurred in subjects with pre-existing cardiovascular conditions.

Within the Malignant or unspecified tumours (SMQ) category, events included anal cancer stage 0, squamous cell carcinoma in-situ lesions of the vulva and vulval cancer (1 subject in the secukinumab Q4W group) and basal cell carcinoma (right clavicle) (1 subject in the secukinumab Q4W group), as reported during Treatment Period 1. In addition, breast carcinoma (1 subject in the Any secukinumab Q2W group) and lung neoplasm and metastatic NSCLC (1 subject in the Any secukinumab Q2W group) were reported.

Other safety topics of interest

Consistent with data from Treatment Period 1, AEs in the category of safety topics of interest were rare during the Entire Study Period and generally balanced between the treatment groups.

New-onset IBD was rare and reported in only 1 subject in the Entire Study Period compared to Treatment Period 1. This subject, in the Any secukinumab Q2W group, presented with Crohn's disease, which was non-serious, of moderate severity and led to study treatment discontinuation.

Neutropenia was also rare with mostly grade 1 or 2 events reported during the Entire Study Period. Grade 3 neutropenia was reported in 1 additional subject (Any secukinumab Q2W) compared to Treatment Period 1 and grade 4 neutropenia was reported in 2 subjects in the Any secukinumab Q4W group. The subject with grade 3 neutropenia had a normal absolute neutrophil count at baseline, and the result of grade 3 neutropenia was an isolated event; the subject's neutrophil count values returned to normal at the subsequent visit. For the 2 subjects with grade 4 neutropenia, these had been single events, the subjects had a normal absolute neutrophil count at baseline and normal values at subsequent visits. All subjects completed treatment and the study.

The incidence of Candida infections (HLT: which mainly consisted of the PTs of oral candidiasis, skin candida and vulvovaginal candidiasis) was low, with an incidence of 4.7% in the Any secukinumab Q2W group and 3.6% in the Any secukinumab Q4W group.

In addition, there were 48 suspected and confirmed cases of COVID-19 reported during the Entire Study Period, with no imbalance across treatment groups. Despite ongoing immunosuppressive secukinumab treatment, the majority of these cases of COVID-19 infection were mild, all cases resolved with conventional therapies, treatment was interrupted in a few cases (n=34) for an average of 4 weeks, with the majority of subjects missing only 1 dose (range: 1 to 8 weeks) and none discontinuing study treatment.

Full 52-week safety dataset

Study M2301

The incidence of AEs within the Infections and infestations SOC during the Entire Study Period was higher in the Any secukinumab Q2W group (52.6%) compared to the Any secukinumab Q4W group (47.6%). Overall, most Infections and infestations (SOC) were non-serious and mild to moderate in severity and recovered without the need for treatment discontinuation.

The most commonly reported infection-related AEs were related to upper respiratory tract infections (HLT), with slightly higher incidence in the Any secukinumab Q2W group compared to the Any secukinumab Q4W group (25.2% and 21.7%, respectively), and mainly (incidence ≥ 5%) consisted of the PTs nasopharyngitis (15.0% in Any secukinumab Q2W; 10.9% in Any secukinumab Q4W) and upper respiratory tract infection (4.5% in Any secukinumab Q2W; 6.4% in Any secukinumab Q4W).

Hypersensitivity (SMQ, narrow) was reported in 13.2% of subjects in the Any secukinumab Q2W group and 12.0% of subjects in the Any secukinumab Q4W group.

Eczema was the most frequently reported AE (3.4% in Any secukinumab Q2W and 3.4% in Any secukinumab Q4W), followed by rash (2.3% in Any secukinumab Q2W and 1.9% in Any secukinumab Q4W), dermatitis (1.5% in Any secukinumab Q2W and 1.9% in Any secukinumab Q4W), and contact dermatitis (1.1% in Any secukinumab Q2W and 2.2% in Any secukinumab Q4W). Most hypersensitivity cases were either mild or moderate, non-serious, generally resolved with treatment and without study treatment discontinuation, and were considered not related to study treatment. No AEs of anaphylaxis were reported.

One new case of suicidal ideation and behavior with the PT of suicidal ideation was reported since the PEA cut-off date (01-Oct-2021) in a subject in the secukinumab Q2W group on Day 278. The event was considered serious, and the drug was interrupted due to the event. The subject had active medical conditions of depression and anxiety ongoing since 2011. The subject was treated with diazepam ethyl loflazepate, venlafaxine, and trazodone. The event was reported as resolving upon treatment and was not suspected by the Investigator and the sponsor to be related to the study treatment. Oncologic disease affecting the subject's spouse, palliative treatment, and spouse's death were listed as contributory factors.

Overall, suicidal ideation and behavior (SMQ) was reported in 2 subjects (0.8%) in the Any secukinumab Q2W group and none in the Any secukinumab Q4W group in the entire study period.

No new malignant or unspecified tumor (SMQ) related event was reported since the PEA data cut-off date (01-Oct-2021). Overall, malignant, or unspecified tumors (SMQ) was reported in 1 (0.4%) subject in the Any secukinumab Q2W group and none in the Any secukinumab Q4W group in the entire study period.

No events related to the risks of neutropenia, major cardiovascular events, Crohn's disease, hepatitis B reactivation, immunogenicity, or interaction with live vaccines were reported during the entire study period.

The Exposure-adjusted incidence rates (EAIRs) of AESIs were comparable between the secukinumab dose groups (Any secukinumab Q2W and Any secukinumab Q4W), except for Infections and infestations (SOC) for which the EAIR was higher in the Any secukinumab Q2W group (98.1 per 100 SY) compared to the Any secukinumab Q4W group (83.2 per 100 SY).

Study M2302

The incidence of AEs within the Infections and infestations (SOC) during the entire study period was similar between the secukinumab treatment groups (52.1% in the Any secukinumab Q2W and 51.5% in the Any secukinumab Q4W). Overall, most Infections and infestations (SOC) that occurred during the entire study period were non-serious and mild to moderate severity and recovered without the need for treatment discontinuation.

The most commonly reported infection-related AEs grouped under the Infections and infestations SOCs was upper respiratory tract infections (HLT) with similar incidence between the secukinumab treatment groups (23.0% in the Any secukinumab Q2W and 20.7% in the Any secukinumab Q4W) and mainly (incidence ≥ 5%) consisted of the PTs nasopharyngitis (10.7% in the Any secukinumab Q2W and 9.4% in the Any secukinumab Q4W group), upper respiratory tract infection (6.1% in the Any secukinumab Q2W and 4.1% in the Any secukinumab Q4W group).

Hypersensitivity (SMQ, narrow) was reported in 10.7% of subjects in the Any secukinumab Q2W group and 8.6% of subjects in the Any secukinumab Q4W group. Eczema was the most frequently reported PT: 4.2% of subjects in the Any secukinumab Q2W and 2.6% of subjects in the Any secukinumab Q4W, followed by dermatitis: 1.5% of subjects in both Any secukinumab Q2W and Any secukinumab Q4W and dermatitis contact: 1.9% of subjects in the Any secukinumab Q2W and 1.1% of subjects in the Any secukinumab Q4W group. Most hypersensitivity cases were either of mild to moderate severity, resolved with treatment, did not lead to study treatment discontinuation, and were considered not related to study treatment. No AEs of anaphylaxis were reported.

No new events were reported since the Week 16 CSR cut-off date. As reported in Study M2302 Week 16 PEA], 1 (0.4%) subject in the Any secukinumab Q4W group reported suicidal ideation and intentional overdose (PTs) on Day 108 compared to none in the Any secukinumab Q2W group. Overall, suicidal ideation and behavior (SMQ) was reported in 1 subject (0.4%) in the Any secukinumab Q2W group and

none in the Any secukinumab Q4W group in the Entire Study Period.

No new malignant or unspecified tumors (SMQ) related event was reported since the cut-off date for the primary efficacy analysis. Overall, malignant, or unspecified tumors (SMQ) were reported in 1 (0.4%) subject in the Any secukinumab Q2W group and 2 (0.8%) subjects in the Any secukinumab Q4W group in the entire study period. No new events were reported since the Week 16 CSR cut-off date.

As reported in the Week 16 CSR, major adverse cardiovascular events (Novartis MedDRA Query) were reported in 2 (0.8%) subjects in the Any secukinumab Q4W group compared to none in the Any secukinumab Q2W group. Both events (myocardial infarction, gastrointestinal hemorrhage) were fatal, in subjects with pre-existing related conditions, and were not suspected to be related to study drug.

No events related to the risks of hepatitis B reactivation or immunogenicity were reported during the entire study period.

Exposure-adjusted incidence rates of AESIs

The Exposure-adjusted incidence rates of AEs were generally comparable between the secukinumab dose regimens (Any secukinumab Q2W and Any secukinumab Q4W) for any Level 1 term.

Pooled data - Safety risks and topics of interest

Infections

AEs in the Infections and infestations (SOC) during the Entire Treatment Period occurred at similar rates in the Any secukinumab groups (52.4% in Q2W and 49.5% in Q4W). Overall, most infections were non-serious and mild to moderate in severity.

Overall, nine subjects reported AEs of infection leading to discontinuation (AEDs), two of which occurred in Treatment Period 1, and seven during the Entire study period. The two subjects (one on secukinumab Q2W and one on placebo) who discontinued during Treatment period 1 are described below:

- the subject in the secukinumab Q2W group discontinued study treatment due to sinusitis (moderate, non-serious, not suspected to be related to study treatment),
- the subject in the placebo group discontinued the study treatment due to upper respiratory tract infection (moderate non-serious, suspected to be related to study treatment).

Seven subjects (4 in the Any secukinumab Q2W and 3 in the Any secukinumab Q4W groups) discontinued due to AEs during the entire study period, details of which are provided below:

1. AEDs in the Any secukinumab Q2W group (4 AEDs in 4 subjects):
    - Ear infection (non-serious, moderate, not suspected to be related to study treatment),
    - Sweat gland infection (serious event of (worsening) of hidradenitis, severe, suspected to be related to study treatment),
    - Large intestine infection (serious, severe, suspected to be related to study treatment),
    - Skin candida infection (serious, severe, suspected to be related to study treatment).
2. AEDs in the Any secukinumab Q4W group (4 AEDs in 3 subjects):
    - Scrotal infection (serious, severe, not suspected to be related to study treatment),
    - Vulvovaginal candidiasis (non-serious, severe, suspected to be related to study treatment),

- Otitis externa fungal (non-serious, severe, suspected to be related to study treatment), and
- Impetigo (non-serious, severe, suspected to be related to the study treatment).

Overall, during the Entire Study Period, there were 17 events by PTs, which were considered serious and occurred in more than one subject in the Any secukinumab group, of which 6 occurred in the Any secukinumab Q2W group and 11 in the Any secukinumab Q4W group. The events by PT reported in the Any secukinumab Q2W group were sweat gland infection (2 subjects, 0.4%), cellulitis, appendicitis, COVID-19 and urinary tract infection (1 subject each, 0.2%). The events reported in the Any secukinumab Q4W group were sweat gland infection (4 subjects, 0.9%), cellulitis and pneumonia (2 subjects each, 0.4%), appendicitis, urinary tract infection, and COVID-19 infection (1 subject each, 0.2%).

Similar to what was described for Treatment Period 1, the more frequently reported infections during the Entire Treatment Period included (described by descending frequency).

- Infections of skin structures (NMQ), with comparable rates within the two secukinumab groups (29.8% in Any secukinumab Q2W, 28.0% in Any secukinumab Q4W) and mainly driven by the events of (worsening of) hidradenitis (11.2% in Any secukinumab Q2W and 11.4% in Any secukinumab Q4W). Of these, 13 cases were considered serious (1.7% in Any secukinumab Q2W, 0.8% in Any secukinumab Q4W).
- Upper respiratory tract infections (by HLT), with higher incidence in the Any secukinumab Q2W group (24.1%) compared to Any secukinumab Q4W (21.2%), and mainly driven by nasopharyngitis (PT).
- Fungal infectious disorders (by HLGT), higher in the Any secukinumab Q2W (12.0%) compared to the Any secukinumab Q4W group (8.3%), which in part may be due to the more severe disease population enrolled in the secukinumab Q2W group and consistent with the inhibition of the IL-17 pathway by secukinumab. Most events in the HS studies corresponded to diverse forms of non-invasive mucocutaneous candidiasis or dermatophytosis. Analysis of 'Candida infections' (by HLT) showed comparable rates across groups (5.5% in the Any secukinumab Q2W group and 4.1% in Any secukinumab Q4W) and mainly consisted of vulvovaginal, oral, and skin candidiasis. Of note, an AE of oesophageal candidiasis was reported in one subject (0.2%) in the Any secukinumab Q4W group. The event was transient (8 days), mild in severity, resolved with treatment with fluconazole and did not lead to treatment discontinuation. The majority of fungal infectious events were managed with topical anti-fungal agents. Except for two AEs that were considered serious or severe, all other AEs were non- serious, non-severe, non-systemic, non-invasive, and did not lead to study treatment discontinuation. The two serious or severe AEs (one each in the secukinumab Q2W and Q4W groups) that led to discontinuation of study drug are:
    - one serious case of skin candida (worsening of inguinal candidial intertrigo) in a subject in the Any secukinumab Q2W in the Treatment Period 2. The event was considered severe, suspected to be related to study treatment and led to discontinuation of the study treatment;
    - one non-serious case of vulvovaginal candidiasis in a subject randomized to secukinumab Q4W in Treatment Period 2. The event was considered severe, suspected to be related to study treatment and led to discontinuation of the study treatment.

One urinary tract candidiasis (candiduria, PT) was reported in a patient in the Any secukinumab Q2W group, 33 days after the 28th IMP administration, during an acute kidney injury SAE and was mild, transient, not related to study treatment, and resolved. Study treatment was not ongoing at the time of the event.

- Infective pneumonia (SMQ, broad) was similar between the secukinumab groups (9.7% in Any

secukinumab Q2W and 10.1% in Any secukinumab Q4W). The broad array of PT events included in this SMQ (i.e., COVID-19, SARS-CoV-2 test positive, suspected COVID-19 or influenza) likely contributed towards the high incidence of Infective pneumonia (SMQ, broad) occurrence. However, these do not reflect the number of confirmed pneumonia cases. In both studies, for the Entire Study Period, 7 pneumonia (PT) cases were reported (3 subjects in the Any secukinumab Q2W group, of which 2 were moderate and 1 was mild; all three were non-serious, and 2 led to study treatment interruption; 3 subjects were in the Any secukinumab Q4W group, of which 2 were severe, 2 were serious, 2 were suspected to be related to the study treatment, and 1 led to study treatment interruption; and 1 subject was in placebo, which was severe, serious, suspected to be related to study treatment, and led to study treatment interruption). Of these 7 pneumonia AEs, 2 were COVID-19-related pneumonia (1 subject in Any secukinumab Q2W, which was mild, non-serious, not suspected to be related to study treatment, and led to study drug interruption; and 1 subject in placebo, which was severe, serious, not suspected to be related to study treatment, resulted in treatment interruption, and recovered/resolved, with the patient having completed the study and moved to the extension study).

Other events of interest within the Infections and infestations SOC included:

- COVID-19: There were 73 suspected and confirmed cases of COVID-19 reported in the Entire Study Period (36 in Any Secukinumab Q2W and 37 in Any Secukinumab Q4W).
- Mycobacterial infectious disorders (HLGT) were reported in two subjects (0.4%) in Any secukinumab Q2W, one in each study. Both cases were mild and not considered related to treatment. One case of confirmed latent TB occurred 17 days after treatment discontinuation; one case of suspected TB did not require specific treatment nor change in study treatment.

All the remaining AEs by HLTs within the 'Infections and infestations' SOC had incidence rates <6%, with no trends in treatment-emergent adverse events or patterns suggesting predominance of either Any secukinumab Q2W or Any secukinumab Q4W.

Hypersensitivity

Analysis of Hypersensitivity (by SMQ, narrow) showed comparable incidence rates for both treatment groups (12.0% in Any secukinumab Q2W and 10.3% in Any secukinumab Q4W). No cases of anaphylaxis were reported in either of the studies. Eczema was the most frequently reported PT, followed by dermatitis, contact dermatitis and rash, of which the majority were mild, not related to study treatment, not leading to study discontinuation, and were managed with standard therapy. One case of dermatitis infected PT which occurred in a subject in Any secukinumab Q4W was considered serious and not related to study treatment.

Malignancies

Analysis of Malignant or unspecified tumours (by SMQ) reported low and comparable crude incidence rates in both secukinumab groups (0.4% in both the Any secukinumab Q2W and Any secukinumab Q4W groups).

A case of breast carcinoma (female, 50-year-old, active smoker: 34 pack-years, smoking duration of 34 years) was diagnosed during the Entire Study Period in a subject in the Any secukinumab Q2W group on Day 316. The study treatment was discontinued due to the event. The event was considered serious and not suspected to be related to study treatment. The event was ongoing at the time of the study discontinuation.

A case of Lung neoplasm and metastatic NSCLC (male, 55 year-old, active smoker: 35 pack- years, smoking duration of 35 years) was diagnosed during the Entire Study Period in a subject from the Any secukinumab Q2W group on Day 263; study treatment was discontinued due to the event, which was considered serious and not suspected to be related to the study treatment.

Major adverse cardiovascular events (MACE)

Major adverse cardiovascular events (by NMQ) were reported in 2 (0.4%) subjects in the Any secukinumab Q4W group. Both events (myocardial infarction, upper gastrointestinal hemorrhage) were fatal, in subjects with pre-existing related conditions and were not suspected to be related to study drug. The case of upper gastrointestinal hemorrhage was included in the MACE category because of the broad scope of the NMQ; however, no major cardiovascular event (MI, stroke, cardiovascular death) was reported in this case. Full narratives were provided.

Suicidal ideation and behavior

Apart from the two cases of Suicide/self-injury (SMQ) reported during Treatment Period 1, one additional case was reported in Study M2301 during the Entire Study Period (PT of 'Suicidal ideation') in the secukinumab Q2W group on study Day 278. The subject had ongoing medical conditions of depression and anxiety at the time of study entry. The event was considered serious and led to drug interruption. The event was reported as not suspected to be related to the study drug, study treatment was reinstituted, the event resolved upon treatment with diazepam, ethyl loflazepate, venlafaxine, and trazodone. The patient moved to the optional extension study.

Other safety topics of interest

- Overall, during the Entire Study Period, new onset IBD occurred in three subjects across both studies (0.3% of randomized subjects in both studies). These AEs included: ulcerative colitis (in the secukinumab Q2W group in Treatment Period 1), IBD (in the secukinumab Q4W group during Treatment Period 1), and Crohn's disease (in the Any secukinumab Q2W group in the Entire Study Period). No new cases of IBD were reported after the Week 16 PEA. All three subjects were in Study M2302. The subjects were on active treatment at the time of the AEs.

- Neutropenia: During the Entire Study Period, cases of neutropenia were rare (42 cases, 4.1%, in the Any secukinumab group), mostly grade 1 or 2, and not associated with infections. There were 11 AEs of neutropenia (neutropenia (PT) or neutrophil count decreased (PT)) reported (6 in Any secukinumab Q2W and 5 in Any secukinumab Q4W), of which 1 was reported since the Week 16 SCS was submitted. None were considered serious, and 2 led to study drug interruption.

Exposure-adjusted incidence rates of safety topics of interest for the Entire Study Period

To account for the fact that not all groups were observed for an equally long time, exposure-adjusted incidence rates (EAIR per 100 subject-years) were also computed for the safety topics of interest derived from the RMP. However, treatment comparisons of secukinumab to placebo for the Entire Study Period must still be interpreted with caution, given that AE rates may not be constant over time.

EAIRs of Infections and infestations (by SOC) were 95.4 per 100 subject-years in the Any secukinumab Q2W group and 88.6 per 100 subject-years in the t the Any secukinumab Q4W group, and both were lower than placebo (127.6 per 100 subject-years).

Consistent with the observations during Treatment Period 1, Infections of skin structures (NMQ) showed lower EAIRs in Any secukinumab compared to placebo (40.9 per 100 subject-years versus 64.6 per 100 subject-years, respectively), and similar EAIRs were seen between the Any secukinumab Q2W and Any secukinumab Q4W groups (42.0 per 100 subject-years versus 39.8 per 100 subject-years, respectively).

Fungal infectious disorders (by HLGT) showed higher EAIR in the Any secukinumab Q2W group (14.8 per 100 subject-years) compared to the Any secukinumab Q4W group (10.2 per 100 subject-years). As mentioned earlier in the document, this may be related to the more severe disease population enrolled in the secukinumab Q2W group, as well as the known role of IL-17A in anti-fungal immunity.

EAIRs for the remaining identified and potential risks and other safety topics of interest did not show relevant predominance for either of the secukinumab groups and were comparable to placebo.

EAIRs per 100 subject-years for SAEs reported for the safety risks were comparable between the treatment groups, and no clinically meaningful differences were noted.

Laboratory findings

Haematology

Treatment Period 1

The majority of newly occurring or worsening laboratory abnormalities in Treatment Period 1 were of CTCAE grade 1 or 2. There were no clinically meaningful differences in the newly occurring or worsening hematology abnormalities across treatment groups during Treatment Period 1.

In Treatment Period 1, neutropaenias were rare, mostly single events and transient. The majority were of grade 1 and 2. Two grade 3 neutropaenias (one in each study) were observed. One subject in the secukinumab Q2W group and one subject in the placebo group, had grade 3 neutropenia (<1.0 - 0.5 x 10E9/L). Both subjects had normal baseline values. The subject on placebo experienced grade 3 neutropenia at Week 16, this was a single event and the subject's neutrophil count returned to normal at a subsequent visit. The subject on secukinumab Q2W with grade 3 neutropenia (single event) improved to grade 2 and 1 (and single normal neutrophils count) at the subsequent visits. Both subjects completed treatment and study. No grade 4 abnormalities were observed in Treatment Period 1.

One subject in the secukinumab Q4W group and 1 subject in the placebo group had grade 3 abnormalities in hemoglobin (<80 g/L). Subject in secukinumab Q4W group had normal baseline value and subject in placebo group had grade 2 hemoglobin values at baseline. The subject in the secukinumab Q4W group with grade 3 hemoglobin discontinued study treatment due to an AE of Inflammatory Bowel Disease. No grade 4 abnormalities were observed.

No meaningful differences in change from baseline in hematological parameters between the secukinumab treatment groups and the placebo group were observed during Treatment Period 1 except for hemoglobin (1.8 g/L for secukinumab Q2W and 1.3 g/L for secukinumab Q4W versus -0.6 g/L for placebo) and platelet (-13.889×10^9/L for secukinumab Q2W and -13.006×10^9/L for secukinumab Q4W versus 7.003×10^9/L for placebo) at the Week 16 visit.

Hematology in Treatment Period 1 for subjects with confirmed or suspected COVID-19 infection

All newly occurring or worsening laboratory abnormalities in Treatment Period 1 were CTCAE grade 1 or 2 for COVID-19 subjects. There were no clinically meaningful differences in the newly occurring or worsening hematology abnormalities across treatment groups during Treatment Period 1 for COVID-19 subjects.

Entire Study Period

Interim (approx. 60%) safety dataset

Similar to the data results in Treatment Period 1, most of the hematological abnormalities reported for the Entire Study Period were grade 1 or 2. There were no clinically meaningful differences in the newly occurring or worsening hematology abnormalities across treatment groups during the Entire Study Period. Apart from the grade 3 abnormalities reported in Treatment Period 1, one additional subject in the Any secukinumab Q2W group had grade 3 anemia at two visits in the Entire Study Period. The subject in the Any secukinumab Q2W group had a grade 1 value at baseline and low hemoglobin values throughout the study and discontinued treatment and the study due to lack of efficacy.

In the Entire Study Period, neutropaenias were rare, mostly grade 1 and 2. Apart from the grade 3 abnormalities reported in Treatment Period 1, one additional subject in the Any secukinumab Q2W group had grade 3 neutropenia and two subjects in the Any secukinumab Q4W group had grade 4 neutropaenias. The subject with grade 3 neutropenia had a normal absolute neutrophil count at baseline and the result of grade 3 neutropenia was an isolated event, the subject's neutrophil count values returned to normal at the subsequent visit. For subjects with grade 4 neutropenia, these had been single events, the subjects had a normal absolute neutrophil count at baseline and normal values at subsequent visits. All subjects completed treatment and study.

There was no difference between the Any secukinumab Q2W and Q4W groups in change from baseline for any of the hematology parameters except for platelets (-9.407 versus -3.774×10^9/L) during the Week 52 visit.

Hematology in Entire Study Period for subjects with confirmed or suspected COVID-19 infection

All newly occurring or worsening hematology abnormalities in the Entire Study Period were CTCAE grade 1 or 2 for COVID-19 subjects. There were no clinically meaningful differences in the newly occurring or worsening hematology abnormalities across treatment groups during the Entire Study Period for COVID-19 subjects.

Full 52-week safety dataset

Study M2301

One new grade 3 abnormality was observed for hematology since the primary endpoint analysis cut-off date (01-Oct-2021). This concerned one subject in the secukinumab Q4W group who had a grade 3 decrease in hemoglobin. This subject entered the study with low hemoglobin value at baseline which remained low (grade 1). At the Week 44 visit, an AE of hemoglobin decreased was noted (grade 3). The AE was not resolved at the time of discontinuation and was not suspected to be related to study treatment.

One new grade 3 abnormality was observed for clinical chemistry since the primary endpoint analysis cut-off date (01-Oct-2021). This concerned one subject in the secukinumab Q2W group who experienced a grade 3 increase in ALT. This subject entered the study with an increased ALT value at baseline (grade 1). The patient’s medical history included severe obesity (BMI: 41) and hyperuricemia. At the Week 52 visit, an AE of liver function test increased was noted (ALT: grade 3; AST: grade 2; bilirubin: grade 1). All other liver function parameters were normal. The subject completed the study treatment and entered the extension study. At the time of study completion, the AE was resolving and was not suspected to be related to study treatment. No subject had abnormalities that met the Hy’s law laboratory criteria in the entire study period.

There were no clinically meaningful differences in the newly occurring or worsening hematology or clinical chemistry including liver function abnormalities across treatment groups during the entire study period.

Most of these abnormalities were of grade 1 or grade 2.

Study M2302

No new grade ≥3 hematological or clinical chemistry or liver function abnormalities were reported since last cut-off date (23-Sep-2021) for the primary endpoint analysis. No subject had abnormalities that met the Hy's law laboratory criteria in the entire study period. There were no clinically meaningful differences in the newly occurring or worsening hematology or clinical chemistry laboratory measurements, including liver function abnormalities across treatment groups, during the entire study period. Most of these abnormalities were of grade 1 or grade 2.

Pooled data

During Treatment Period 1 and the Entire Study Period, the majority of newly occurring or worsening laboratory abnormalities were of CTCAE grade 1 or 2; grade 3 and grade 4 abnormalities occurred in ≤ 2 subjects in any of the secukinumab groups. There were no clinically meaningful differences in the newly occurring or worsening hematology abnormalities across treatment groups during the Entire Study Period.

There was a total of 4 grade 3 laboratory abnormalities of decreased hemoglobin count reported in both M2301 and M2302 studies (3 in the Any secukinumab group and 1 in the placebo treatment group). Of these, 2 were reported in Treatment period 1 (1 in secukinumab Q4W and 1 in placebo) and 2 in the Entire Study period (1 in Any secukinumab Q2W and 1 in Any secukinumab Q4W). The new grade 3 abnormality reported since the Week 16 SCS cut-off is described below:

- One subject with grade 3 hemoglobin decrease in the secukinumab Q4W group in study M2301 (at three visits in the Entire Study Period) had a grade 1 value at baseline and low hemoglobin values throughout the study. Due to the progressive lowering of hemoglobin values, the subject underwent gastroscopy and colonoscopy procedures, which revealed abnormal findings (details not available) the subject was administered one dose of intravenous iron preparation. The last available value (72 g/L) was measured at Week 60 (safety follow up visit), and the subject completed the study treatment.

In the Entire Study Period in both Studies M2301 and M2302, laboratory abnormalities of low neutrophil count were rare (n = 42, 4.0%), mostly grade 1 or 2. There were 3 subjects with grade 3 decrease in neutrophil count (2 in secukinumab Q2W and 1 in placebo), of which two were noted in Treatment Period 1 (1 on Secukinumab Q2W and 1 on placebo). Two subjects in the Any secukinumab Q4W group had grade 4 neutropenia. No new grade 3 or grade 4 neutrophil abnormalities were reported since the SCS cut-off. In both Studies M2301 and M2302, there was no clinically relevant change from baseline in hematological parameters up to Week 52 in either secukinumab treatment group.

Clinical chemistry

Treatment Period 1

Most of the newly occurring or worsening chemistry laboratory abnormalities during Treatment Period 1 were CTCAE grade 1 or 2. There were no clinically meaningful differences in the newly occurring or worsening clinical chemistry abnormalities across treatment groups during Treatment Period 1. One subject in the secukinumab Q2W group had grade 3 ALT and one subject each in the secukinumab Q2W and secukinumab Q4W groups had grade 3 AST. Two subjects in secukinumab Q4W and 1 subject in placebo had grade 3 GGT abnormalities. The subject in the secukinumab Q2W group (in Study M2301) had grade 3 ALT and AST at a single visit and the results returned to normal at the subsequent visit. The subject was continuing in the study at the time of data cut-off. The subject in the secukinumab Q4W group (in Study M2302) with grade 3 AST had normal baseline results and the AST result returned to normal at the subsequent visit. The subject discontinued treatment in Treatment Period 2 due to lack of

efficacy. For both subjects with grade 3 GGT abnormalities in the secukinumab Q4W (one in each study), these were isolated events and the GGT values returned to normal or improved at the subsequent visits. One subject completed the study and moved to the extension study while the second subject discontinued treatment due to an AE of suicidal ideation. The subject in the placebo group with grade 3 GGT abnormalities had high GGT values at all visits (including baseline). The subject completed the study and moved to the extension study. There were no grade 4 abnormalities.

There was no meaningful difference between the secukinumab groups and placebo in change from baseline up to Week 16 for any of the chemistry parameters except for ALP (-3.0 for secukinumab Q2W and -3.1 for secukinumab Q4W versus 0.2 U/L for placebo) and GGT (-2.4 for secukinumab Q2W and -2.2 for secukinumab Q4W versus 1.2 U/L for placebo).

Clinical chemistry in Treatment Period 1 for subjects with confirmed or suspected COVID-19 infection

All newly occurring or worsening clinical chemistry abnormalities in Treatment Period 1 were CTCAE grade 1 or 2 for COVID-19 subjects. There were no clinically meaningful differences in the newly occurring or worsening clinical chemistry abnormalities across treatment groups during Treatment Period 1 for COVID-19 subjects.

Entire Study Period

Interim (approx. 60%) safety dataset

Similar to the results in Treatment Period 1, the majority of chemistry abnormalities were grade 1 or 2, with a few grade-3 events. There were no clinically meaningful differences in the newly occurring or worsening clinical chemistry abnormalities across treatment groups during the Entire Study Period.

Apart from the grade 3 ALT increase during Treatment Period 1, one additional subject in the Any secukinumab Q2W group and two subjects in the Any secukinumab Q4W group had a grade 3 increase in ALT in the Entire Study Period. The subject in the Any secukinumab Q2W group (in Study M2302) with grade 3 ALT abnormality at Week 20 and Week 28 visits, had high ALT values at all visits (including grade 1 values at baseline), the subject was continuing in the study at the time of data cut-off and no data for a subsequent visit after Week 28 (from when the last grade 3 ALT abnormality was noted) was available. The subject in the Any secukinumab Q4W group (in Study M2301) had an ongoing hepatobiliary disorder, the ALT results were high for the majority of visits however, the grade 3 ALT abnormality was observed at a single visit only. The patient completed the treatment and the study. The subject in the Any secukinumab Q4W group (in Study M2302) was continuing in the study at the time of data cut-off and no data for a subsequent visit (from when grade 3 ALT abnormality was noted) was available. Apart from the two subjects with grade 3 AST increases (one in each of the secukinumab groups) during Treatment Period 1, two subjects in Any secukinumab Q2W and one subject in Any secukinumab Q4W (all in Study M2302) had a grade 3 AST abnormality during the Entire Study Period. Both subjects in the Any secukinumab Q2W group switched treatment from placebo in Treatment Period 2, grade 3 AST abnormality was an isolated event and the AST results either returned to normal or improved at the subsequent visit. Both subjects were ongoing in the study at the time of data cut-off. The subject in the Any secukinumab Q4W group was continuing in the study at the time of data cut-off and no data for a subsequent visit (from when grade 3 AST abnormality was noted) was available. In the Entire Study Period, apart from the grade 3 GGT increases during Treatment Period 1, one subject each in the Any secukinumab Q2W group and in the Any secukinumab Q4W group had a grade 3 GGT increase. For both subjects the grade 3 abnormality was an isolated event, one subject completed the treatment and the study, and one subject completed the treatment but discontinued the study due to Physician decision (due to COVID-19). One subject in the Any secukinumab Q4W group (in Study M2301) with an active condition of non-alcoholic steatohepatitis at baseline had grade 4 GGT abnormality. The subject's GGT

values were high throughout the study (with a reported AE of worsening of NASH) with a baseline grade 2 GGT. The grade 4 abnormality was an isolated event that occurred at the Week 52 visit after which the subject completed the study treatment and moved to the extension study.

There was no meaningful difference between the Any secukinumab Q2W and Q4W groups in change from baseline up to Week 52 for any of the chemistry parameters except for GGT (0.3 versus 1.8 U/L).

Full 52-week safety dataset

Study M2301

One new grade 3 abnormality was observed for clinical chemistry since the primary endpoint analysis cut-off date (01-Oct-2021). This concerned one subject in the secukinumab Q2W group who experienced a grade 3 increase in ALT. This subject entered the study with an increased ALT value at baseline (grade 1). The patient's medical history included severe obesity (BMI: 41) and hyperuricemia. At the Week 52 visit, an AE of liver function test increased was noted (ALT: grade 3; AST: grade 2; bilirubin: grade 1). All other liver function parameters were normal. The subject completed the study treatment and entered the extension study. At the time of study completion, the AE was resolving and was not suspected to be related to study treatment. No subject had abnormalities that met the Hy's law laboratory criteria in the Entire Study Period.

There were no clinically meaningful differences in the newly occurring or worsening clinical chemistry including liver function abnormalities across treatment groups during the Entire Study Period. Most of these abnormalities were of grade 1 or grade 2.

Study M2302

No new grade ≥3 clinical chemistry or liver function abnormalities were reported since last cut-off date (23-Sep-2021) for the primary endpoint analysis. No subject had abnormalities that met the Hy's law laboratory criteria in the Entire Study Period. There were no clinically meaningful differences in the newly occurring or worsening hematology or clinical chemistry laboratory measurements, including liver function abnormalities across treatment groups, during the Entire Study Period. Most of these abnormalities were of grade 1 or grade 2.

Clinical chemistry in the Entire Study Period for subjects with confirmed or suspected COVID-19 infection

All newly occurring or worsening clinical chemistry abnormalities in Treatment Period 1 were CTCAE grade 1 or 2 for COVID-19 subjects. There were no clinically meaningful differences in the newly occurring or worsening clinical chemistry abnormalities across treatment groups during the Entire Study Period for COVID-19 subjects.

Pooled data

There were no clinically meaningful differences in the newly occurring or worsening clinical chemistry abnormalities across treatment groups during Treatment Period 1 or in the Entire Study period. Most of the newly occurring or worsening chemistry laboratory abnormalities in Treatment Period 1 and in the Entire Study Period were CTCAE grades 1 or 2. Grade 3 elevations were few and occurred in ≤3 subjects in any of the secukinumab treatment groups (Q2W or Q4W). There was one grade 4 elevation in GGT in a subject in the Any secukinumab Q4W group.

A total of 5 grade 3 laboratory ALT elevations were reported in both M2301 and M2302 studies in the Entire Study Period (3 in Any secukinumab Q2W and 2 in Any secukinumab Q4W). Of these, 1 was reported in Treatment period 1 (in secukinumab Q2W). The new grade 3 abnormality reported since the Week 16 SCS cut-off is described below:

- One subject in the Any secukinumab Q2W group in M2301 with grade 3 ALT abnormality at Week 52 had increased ALT values at all visits (including grade 1 values at baseline). An AE of Liver function test (PT) increased was reported on the same day (moderate, non-serious, not suspected to be related to study treatment). The subject completed the study and moved to the extension study.

No ALT grade 4 abnormalities were reported.

A total of 5 grade 3 laboratory AST elevations were reported in both M2301 and M2302 studies in the Entire Study period (3 in Any secukinumab Q2W and 2 in Any secukinumab Q4W). Of these, 2 were reported in Treatment period 1 (one in each of the secukinumab groups). No new grade 3 abnormalities were reported since the Week 16 SCS cut-off. No AST grade 4 abnormalities were reported.

A total of 5 grade 3 laboratory GGT elevations were reported in both M2301 and M2302 studies in the Entire Study Period (1 in Any secukinumab Q2W, 4 in Any secukinumab Q4W). Of these, 3 were reported in Treatment period 1 (2 in secukinumab Q4W and 1 in placebo). As reported in the SCS, one subject had a grade 4 GGT abnormality at the Week 52 visit, after which the subject completed the study treatment and moved to the extension study, the subject had a grade 2 value at baseline and high GGT values throughout the study. No new grade 3 or grade 4 GGT abnormalities were reported since the SCS cut-off.

The incidence of liver enzyme abnormalities during Treatment Period 1 and the Entire Study Period was low and generally comparable between the treatment groups. No clinically meaningful changes in liver enzymes were observed. No subjects had abnormalities that met the Hy's law laboratory criteria. Isolated cases of ALT or AST or other liver enzymes with meaningful increases (e.g., ≥3x ULN) occurred.

Clinical chemistry in the Entire Study Period for subjects with confirmed or suspected COVID-19 infection

All newly occurring or worsening clinical chemistry abnormalities in Treatment Period 1 were CTCAE grade 1 or 2 for COVID-19 subjects. There were no clinically meaningful differences in the newly occurring or worsening clinical chemistry abnormalities across treatment groups during the Entire Study Period for COVID-19 subjects.

Vital signs, physical findings, and other observations related to safety

No pooled analyses for vital signs were performed, but the individual study results were provided. The incidence of vital sign abnormalities was low, and no clinically meaningful difference was observed between the treatment groups.

Safety in special populations

According to the MAH, safety analyses were not conducted for any particular special patient population.

Subgroups of study population

AEs and SAEs (including key risk AEs) were evaluated for Treatment Period 1 and the Entire Study Period according to the following subgroups based on demography (age, gender, race), baseline characteristics (disease duration, body weight), current antibiotic use, geographical region, previous exposure to biologics and smoking status.

Of note, individual events in some of these subgroups were reported in small numbers. Therefore, caution should be applied when attempting to draw meaningful conclusions on differences in event incidence by treatment regimen among these subgroups.

Intrinsic factors

The following subgroups based on intrinsic demographic and baseline disease factors were evaluated:

- Age: <40 years (N=692), ≥40 years (N=392) [AIN457M SCS-Section 5.1.1.1]
- Gender: Male (N=474), female (N=610) [AIN457M SCS-Section 5.1.1.2]
- Race: White (N=845), Black or African American (N=86), Asian (N=117), American Indian or Alaska Native (N=24), Native Hawaiian or Other Pacific Islander (N=1), Multiple (N=10), Not reported (N=1) [AIN457M SCS-Section 5.1.1.3]
- Disease duration: <2 years (N=48), 2 to <5 years (N=189), 5 to <10 years (N=266), ≥10 years (N=581) [AIN457M SCS-Section 5.1.1.4]
- Body weight (2 categories): <90kg (N=512), ≥90 kg (N=572) [AIN457M SCS-Section 5.1.1.5]
- Body weight (3 categories): <70 kg (N=163), 70 to <90 g (N=349), ≥90 kg (N=572) [AIN457M SCS-Section 5.1.1.6]

Extrinsic factors

The following subgroups based on extrinsic demographic and baseline disease factors were evaluated:

- Current antibiotic use: Yes (N=127), no (N=957)
- Geographical region: AMEA (N=145), RE (N=670), LaCAN (N=82), US (N=165), Japan (N=22)
- Previous exposure to biologics: Yes (N=255), no (N=829)
- Smoking status: Never (N=334), current (N=585), former (N=165)

Analysis of adverse effect exposure-response information

Overall, the safety profiles for the secukinumab 300 mg Q2W group and the secukinumab 300 mg Q4W group were comparable. The overall incidence rate of AEs was higher in Any secukinumab Q4W compared to Any secukinumab Q2W (266.4 per 100 subject-years in Any secukinumab Q2W, 306.0 per 100 subject-years in Any secukinumab Q4W), which does not suggest a dose relationship overall. AEs in the Infections and infestations SOC occurred at a slightly higher incidence in the Any secukinumab Q2W group (92.5 per 100 subject-years) compared to the Any secukinumab Q4W group (84.1 per 100-subject-years).

Data from previous studies and past submissions also support the assertion that differences in loading or dosing regimens do not impact the safety profile of secukinumab. At the time of study initiation, the secukinumab 300 mg Q2W regimen had been tested in approximately 120 subjects for at least 24 weeks in completed clinical studies in uveitis and PsO. Recently available results from additional 196 subjects on the secukinumab 300 mg Q2W regimen in Study A2324, conducted in adults with moderate to severe plaque PsO with a body weight ≥90 kg who were treated with secukinumab Q4W vs. secukinumab Q2W dosing regimens showed that the safety profile of secukinumab 300 mg Q2W was similar to that of secukinumab 300 mg Q4W. The safety profile of secukinumab 300 mg Q2W was observed to be in-line with that of secukinumab 300 mg Q4W.

The pooled HS data reveal no new safety concerns specific to the secukinumab 300 mg Q2W and Q4W regimens.

To further evaluate the safety of the secukinumab dose regimens in subjects with HS, exposure-response safety analyses were conducted for the pooled database of Studies M2301 and M2302 on subjects randomized to secukinumab Q2W or Q4W (n=721). These analyses focused on two types of AEs: Infections and infestations (SOC) and Candida infections (HLT).

The incidence rate of AEs at 1 year was summarized by the range of average secukinumab concentrations at steady state and showed that there were no differences in the incidence rates of Infections and infestations (SOC) or Candida infections (HLT) across the secukinumab concentration groups. Logistic regression analysis indicated that the predicted incidence rates of these events were generally stable with increasing secukinumab concentration.

Immunogenicity and immunological events

An electrochemiluminescence-based method was used for the detection of potential anti secukinumab antibody formation. Blood samples for determination of anti-drug-antibodies (ADA) were taken pre-dose at the scheduled time points as indicated in protocols of individual Studies M2301 and M2302. Treatment-emergent anti-drug-antibodies (TE-ADA) are defined as ADA that developed post-treatment in subjects with negative ADA screens at baseline (i.e., seroconversion to ADA positivity from a seronegative state). There was a TE-ADA incidence of <1% in the HS patient population who started treatment at the beginning of the study. In Study M2301, treatment-emergent ADAs were reported in 1 subject in the secukinumab Q4W group during the follow-up period (Week 60). In Study M2302, treatment-emergent ADAs were reported in 2 subjects in the secukinumab Q2W group (1 subject at Week 16 and 1 subject during the follow-up period). Treatment-emergent ADAs in these subjects were not associated with loss of efficacy or AEs related to immunogenicity. In Study M2302, PK behavior was normal in the 2 subjects with treatment-emergent ADAs.

Non-treatment-emergent ADA were also observed in both studies. In Study M2301, 4.6% and 2.9% of secukinumab naïve subjects were ADA positive at baseline only in the Q2W and Q4W arms, respectively. In Study M2302, 2.9% and 2.3% of secukinumab naïve subjects were ADA positive at baseline only in the Q2W and Q4W arms, respectively. Non-treatment related, naturally occurring ADA may lead to a confirmed positive response in this assay in either pre-dose samples or samples derived from patients not treated with secukinumab.

Safety related to drug-drug interactions and other interactions

No new information regarding drug interactions was generated in Study M2301 and Study M2302.

Live vaccines should not be given concurrently with secukinumab.

Subjects receiving secukinumab may receive concurrent inactivated or non-live vaccinations. In the vaccine Study CAIN457A2224, after meningococcal and inactivated influenza vaccinations were administered to healthy volunteers, a similar proportion of subjects treated with secukinumab, and subjects treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titers to meningococcal and influenza antigens. The data suggest that secukinumab does not suppress the humoral immune response to the meningococcal or influenza vaccines.

Discontinuation due to adverse events

Treatment Period 1

The incidence of AEs leading to study treatment discontinuation was low and comparable in both secukinumab Q2W and Q4W groups (1.7% and 1.4%), and the placebo group (1.4%). None of the AEs that led to study treatment discontinuation were reported in >1 subject (by PT) in any treatment group. In total, 11 subjects in the Any secukinumab group (6 subjects in the secukinumab Q2W group and 5 subjects in the secukinumab Q4W group) discontinued study treatment due to the following AEs: arthralgia, ulcerative colitis, IBD, dermatitis, amyloidosis, PsO, rheumatoid arthritis, sinusitis, vulval cancer, suicidal attempt, and suicidal ideation (each reported in 1 subject). Of these, the AEs of ulcerative

colitis, IBD, suicide attempt and amyloidosis were considered serious. In the placebo group, 5 subjects reported AEs of upper respiratory tract infection, hematuria, hidradenitis, human chorionic gonadotropin increased and pruritus (each reported in 1 subject) that led to study treatment discontinuation. None of these AEs were considered serious.

Entire Study Period

Interim (approx. 60%) safety dataset

The incidence of AEs leading to study drug discontinuation (**Table 40**) was low and comparable in the secukinumab Q2W and Q4W groups (4.7% vs. 4.2%), the Any secukinumab Q2W vs. Q4W groups (4.0% vs. 3.4%) and the placebo group (3.7%). Two AEs caused discontinuation in >1 subject in total: (worsening of) hidradenitis in 3 subjects in the Any secukinumab Q2W group and 2 subjects in the Any secukinumab Q4W group, and abdominal pain in 1 subject each in the Any secukinumab Q2W and Q4W groups. The events of (worsening of) hidradenitis and abdominal pain were serious. AEs of (worsening of) hidradenitis were mostly events of worsening of study indication or flares of HS. All other PTs were isolated events with each reported in no more than 1 subject. In total, 21 subjects in the Any secukinumab Q2W group and 18 subjects in the Any secukinumab Q4W group discontinued study treatment due to AEs.

Table 40 Deaths, other serious or clinically significant adverse events or related discontinuations - Entire Study Period (Safety set)

	AIN457 Q2W N=361 n (%)	AIN457 Q4W N=360 n (%)	Any AIN457 Q2W N=527 n (%)	Any AIN457 Q4W N=533 n (%)	Any AIN457 N=1060 n (%)
Subjects with any AE(s)	294 (81.4)	295 (81.9)	405 (76.9)	422 (79.2)	827 (78.0)
Subjects with serious or other significant events					
Death	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.4)	2 (0.2)
Non-fatal SAE(s)	27 (7.5)	22 (6.1)	35 (6.6)	38 (7.1)	73 (6.9)
Discontinued study treatment due to any AE(s)	17 (4.7)	15 (4.2)	21 (4.0)	18 (3.4)	39 (3.7)

Source: AIN457M SCS-Table 2-7

Full 52-week safety dataset

In the entire study period, the incidence of AEs causing discontinuation was comparable between the Any secukinumab Q2W and Q4W groups.

Study M2301

No additional subjects who discontinued study treatment due to AEs were reported since the Week 16 PEA cut-off date (01-Oct-2021).

Overall, the incidence of AEs leading to discontinuation was low and similar in both Any secukinumab Q2W and Q4W groups. In total, 11 subjects (4.1%) in the Any secukinumab Q2W group discontinued study treatment due to AEs compared to 7 subjects (2.6%) in the Any secukinumab Q4W group. All these events were isolated incidences, and each of them were reported in no more than 1 subject. At the final DBL, in 3 subjects (1 each in the secukinumab Q2W (PT: hidradenitis), secukinumab Q4W (PT: hidradenitis), and placebo-Q2W (PT: hematemesis) groups) the action taken with study treatment due to AE was updated compared to the Week 16 PEA from "drug withdrawn" to "dose not changed".

At time of the final DBL, the action taken with the study treatment due to AE (ear infection) was updated from "drug interrupted" to "drug withdrawn" in 1 subject in the secukinumab Q2W group, and one additional AE (PT: impetigo) leading to discontinuation was reported for a subject in the placebo-Q4W

group who had already reported treatment discontinuation due to an AE of fungal external otitis (i.e., subject discontinued treatment due to these two AEs).

Study M2302

At the time of the final DBL, no additional subjects who discontinued study treatment due to AEs were reported since the Week 16 PEA cut-off date (23-Sep-2021).

As reported in the Week 16 CSR, the incidence of AEs leading to discontinuation was low and similar in both the Any secukinumab Q2W and the Any secukinumab Q4W groups. At Week 52 final analysis, nine (3.4%) subjects in the Any secukinumab Q2W group discontinued study treatment due to AEs compared to 10 (3.8%) subjects in the Any secukinumab Q4W group. All these events were isolated incidences, each reported in only one subject, and the majority of them were not suspected to be related to study treatment.

Post marketing experience

Secukinumab is currently not approved for moderate to severe HS.

Post-marketing data for the other approved indications are provided in AIN457 PSUR 26-Dec-2019 to 25-Dec-2020. The cumulative post-marketing subject exposure since the International Birth Date (IBD, 26-Dec-2014) of secukinumab is estimated to be approximately 680,470 subject-treatment years.

2.5.1. Discussion on clinical safety

The main safety data in support of the extension of indication of secukinumab to moderate to severe HS derive from the two randomized, double-blind, multicenter pivotal phase 3 studies of identical design, study M2301 and study M2302, assessing two subcutaneous secukinumab dose regimens (300 mg Q2W or Q4W). Pooled data are presented to assess short-term (16 weeks - Treatment Period 1) and long-term safety (52 weeks - Entire Study Period) up to the data cut-off dates (01-Oct-2021 for Study M2301 and 23-Sep-2021 for Study M2302). In the initial submission, pooled safety data were available for at least 16 weeks of treatment for all subjects and the long-term data up to 52 weeks for approximately 60 %. Subsequently, the full 52-week safety dataset was submitted for assessment. However, these data were made available only separately for each pivotal study. Therefore, pooled data were subsequently, on request, provided.

For both dosing regimens, secukinumab 300 mg was administered at Weeks 0, 1, 2, 3 and 4 as loading injections, followed by maintenance injections on a Q2W or Q4W basis, up to Week 52 as per protocol schedule.

As the Q2W administration of secukinumab 300 mg has recently been approved for use in PsO patients in the EU, a comparison to available safety data from Study A2324 was performed.

In addition, the MAH refers also to the existing secukinumab safety database across all other indications, with a cumulative exposure of 34,907.50 subject-years from 20,961 subjects and healthy volunteers in clinical studies, and 680,470 subject-years of post-marketing exposure to secukinumab (AIN457 PSUR 26-Dec-2019 to 25-Dec-2020).

Furthermore, an extension study M2301E1 is currently ongoing; the CHMP recommends the MAH to submit these results for assessment once they become available.

Patient exposure

Treatment period 1 (16 weeks)

Exposure to study treatment was summarized for the pooled data from both of the phase 3 studies PEP analysis. In total, 721 subjects received secukinumab in the placebo-controlled Treatment Period 1 (361 subjects in secukinumab Q2W and 360 subjects in secukinumab Q4W) and 363 subjects received placebo.

Overall, 93.6% of the randomized subjects completed Week 16 of the studies.

Pooled long-term data from the two pivotal studies
In total, 1060 adult subjects with moderate to severe HS received secukinumab during the Entire Study Period (527 subjects in Any secukinumab Q2W and 533 subjects in Any secukinumab Q4W).

At Week 16, subjects who were initially randomized to either of the two secukinumab regimens continued on the same dose regimen, and subjects initially randomized to Placebo were randomized to either secukinumab Q2W or Q4W, following a blinded loading dose regimen. Therefore, both the 'Any secukinumab Q2W' and 'Any secukinumab Q4W' groups also included placebo-switchers assigned to these regimens, and the treatment group 'Any secukinumab' included all subjects who took at least one dose of secukinumab.
In the Entire Study Period, the median duration of exposure was 364.0 days for the Any secukinumab treatment group, with a cumulative exposure of 907.0 subject-years. For subjects who switched from placebo to secukinumab at Week 16, exposure only after the first dose of secukinumab is counted.

Cumulative exposure (subject-years) was similar between the secukinumab Q2W (340.2) and Q4W (336.5) groups and similar between the Any secukinumab Q2W group (454.0) and Any secukinumab Q4W group (453.0).

Although disease history and baseline characteristics were generally balanced across the treatment groups, the secukinumab Q2W group comprised a more severe population (more subjects with Hurley stage III, higher lesion count, older age, more smokers, and more subjects rated ‘very severe’ on the HS-PGA) compared to the secukinumab Q4W and placebo groups. Despite these differences between treatment groups, the demographics of the overall population were, according to the MAH, consistent with the population of subjects who completed the Week 52 visit up to the data cut-off date for each study.

Treatment emergent adverse events (TEAEs)

A direct safety comparison between secukinumab and placebo can be evaluated up to 16 weeks of the *Treatment Period 1*. The overall incidence of AEs was similar between the secukinumab treatment groups (65.1% and 64.4% in the secukinumab Q2W and Q4W groups, respectively) and the placebo group (65.0%). No meaningful differences in AE frequency or clinical relevance were reported between the secukinumab Q2W and Q4W groups. AEs were mostly non-serious (approximately 98%), mild to moderate in severity (approximately 97%), and did not require drug discontinuation (approximately 99%).

The AEs with the highest frequency were reported in the SOC of Infections and infestations, with similar incidences across the secukinumab groups (30.7% vs. 30.6% in the secukinumab Q2W and Q4W groups, respectively) and placebo group (31.7%), with the most commonly reported AEs being headache (10.4%), nasopharyngitis (8.0%) and (worsening of) hidradenitis (5.1%).

Initial interim (60%) 52-week *Entire Study Period* (from week 16 onward all patients receiving secukinumab), showed, after adjusting for exposure, that overall incidence of AEs was lower in the Any secukinumab group than the placebo group (285.2 vs. 412.2 per 100 subject-years). The EAIR rate was lower for the secukinumab Q2W group compared to the secukinumab Q4W group (274.3 vs. 296.7 per 100 subject-years) and for the Any secukinumab Q2W group compared to the Any

secukinumab Q4W group (266.4 vs. 306.0 per 100 subject-years). Any possible reasons for the apparent differences seen, were not readily apparent. However, placebo comparison in the Entire Treatment Period is hampered by the different duration of treatment.

The SOC with the highest EAIR in the Any secukinumab group was Infections and infestations. A higher incidence was reported in the Any secukinumab Q2W group compared to the Any secukinumab Q4W group (92.5 vs. 84.1 per 100 subject-years), with the most reported PT being nasopharyngitis. No differences were observed in the EAIRs of other SOCs between the secukinumab dose regimens.

The most commonly reported (≥10 per 100 subject-years) AEs by PT in the Any secukinumab group were headache (20.9 per 100 subject-years), (worsening of) hidradenitis and nasopharyngitis (both 14.8 per 100 subject-years). On PT level, no meaningful differences in AE frequency or clinical relevance were reported between the secukinumab Q2W and Q4W groups, with the majority (approximately 98%) of the reported AEs being non-serious, mild to moderate in severity (approximately 97%) not requiring drug discontinuation (approximately 99%).

On analysis of the full 52-week safety Entire Study Period dataset, there were no new treatment-emergent safety signals identified during the long-term exposure of secukinumab, with the safety profile over the entire study period being similar to Treatment Period 1. The overall incidence of AEs for both treatment groups was 83.9% in study M2301 and 80.8% in study M2302. Subsequently, pooled data were provided, on request.

Consistent with data reported at Week 16, for the Entire Study Period, the overall EAIR for AEs was lower in the Any secukinumab Q2W group (274.6 per 100 subject-years) compared to the Any secukinumab Q4W group (301.6 per 100 subject-years), with no specific SOCs or PTs driving the difference. 'Infections and infestations' was the most commonly reported SOC with a higher incidence in the Any secukinumab Q2W group (94.0 per 100 subject-years) compared to the Any secukinumab Q4W group (87.9 per 100 subject-years). Most of the individual events in the SOC 'Infections and infestations' (>96%) were non-serious, mild (approximately 70%) or moderate (approximately 28%) in severity and did not lead to treatment discontinuation (only approximately 1% of AEs resulted in permanent treatment withdrawal). As was reported at Week 16, the most frequent AEs over the Entire Study Period (>5%) included headache, (worsening of) hidradenitis, nasopharyngitis, diarrhea and upper respiratory tract infection, with similar frequencies between the Any secukinumab Q2W and Q4W groups.

Treatment emergent adverse drug reactions (TEADRs)

Pooled Phase 3 data of studies conducted in HS and other relevant indications (i.e., psoriasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis) to update the current list of adverse drug reactions (ADRs) for secukinumab did not reveal any new ADRs and support the previously established safety profile of secukinumab across the approved indications. A concise tabular presentation of the TEADRs (including severity) of the pooled safety data (full 52 week data set) of the two pivotal phase 3 studies was, on request, provided by the MAH. Section 4.8 of the SmPC has been updated with the pooled numbers. In addition the frequency for the adverse reaction tinea pedis has been updated in section 4.8 of the SmPC from common to uncommon and details on infections for patients with HS are provided.

Deaths, SAE

No deaths were reported during Treatment Period 1. The incidence rates of SAEs up to 16 weeks were low and comparable for both secukinumab regimens and placebo (2.5% for both secukinumab Q2W and secukinumab Q4W versus 3.0% for placebo). No pattern in the type of event was evident. As expected, the most common SAEs for secukinumab, observed in both study periods, were in the Infections and infestations SOC.

In the Entire Study Period (full pooled dataset), the two deaths reported were considered unrelated to the study drug. The incidence of SAEs was low and comparable for both secukinumab groups (7.6% in Any secukinumab Q2W, 7.5% in Any secukinumab Q4W), with no clustering or pattern in the type of events reported.

In the analysis of the full safety dataset several new SAEs were reported. Differences in the numbers of SAEs between treatment groups was minimal and all these SAEs were not suspected by the investigator to be related to study treatment. No clinically meaningful differences in the EAIRs of total SAEs were observed across the treatment groups (9.4 per 100 subject-years in Any secukinumab and 10.1 per 100 subject-years in placebo) nor between the secukinumab dose regimen groups (9.1 per 100 subject-years in Any secukinumab Q2W and 9.6 per 100 subject-years in Any secukinumab Q4W).

Discontinuations

During Treatment Period 1, the incidence of AEs leading to study treatment discontinuation was low, single occurrences and comparable in both secukinumab Q2W and Q4W groups (1.7% and 1.4%), and the placebo group (1.4%). In total, 11 subjects in the Any secukinumab group (6 subjects in the secukinumab Q2W group and 5 subjects in the secukinumab Q4W group) discontinued study treatment due to the following AEs: arthralgia, ulcerative colitis, IBD, dermatitis, amyloidosis, PsO, rheumatoid arthritis, sinusitis, vulval cancer, suicidal attempt, and suicidal ideation (each reported in 1 subject). Of these, the AEs of ulcerative colitis, IBD, suicide attempt and amyloidosis were considered serious. In the placebo group, 5 subjects reported AEs of upper respiratory tract infection, hematuria, hidradenitis, human chorionic gonadotropin increased and pruritus that led to study treatment discontinuation. None of these AEs were considered serious.

In the full 52-week dataset, no additional subjects who discontinued study treatment due to AEs were reported since the Week 16. Overall, the incidence of AEs leading to discontinuation was low and similar in both Any secukinumab Q2W and Q4W groups. All these events were isolated incidences, and each of them were reported in no more than one subject. At the final DBL, the reason for discontinuation was reclassification for 3 subjects, but this is considered not to have an impact on the interpretation of these data.

Severity of AEs

Adverse events during both Treatment Period 1 and the Entire Study Period were mostly mild or moderate in severity, with no imbalance seen in the severity of AEs between the secukinumab and the placebo groups. The proportion of subjects with mild AEs during the Entire Study Period in the secukinumab groups were 38.5% in Any secukinumab Q2W and 41.7% in Any secukinumab Q4W, and those with moderate AEs were 35.9% in Any secukinumab Q2W and 34.7% in Any secukinumab Q4W groups. Severe events were reported with similar incidence in the Any secukinumab Q2W and Any secukinumab Q4W groups (7% and 6.9%, respectively). The most frequent severe AEs reported for both the secukinumab groups were in the SOC 'Infections and infestations' (2.7% in Any secukinumab Q2W and 2.1% in Any secukinumab Q4W). All severe AEs (PTs) were in ≤3 subjects, with the exceptions of the following: worsening of Hidradenitis (4 subjects in Any secukinumab Q2W and 7 subjects in Any secukinumab Q4W) considered not related to study treatment (except in one subject), and not leading to study treatment discontinuation. Three cases occurred before starting study treatment; headache (3 subjects in Any secukinumab Q2W and 1 subject in Any secukinumab Q4W): considered related in one case, with all subjects completing the study with no treatment interruption; and sweat gland infection (4 subjects in Any secukinumab Q2W and 1 subject in Any secukinumab Q4W), considered related in one case. All subjects completed the study, with 1 subject interrupting and 1 subject discontinuing the study treatment.

Laboratory values

Overall, no clear safety signals were observed on analysis of the laboratory data. The majority of newly occurring or worsening laboratory abnormalities in Treatment Period 1 were of CTCAE grade 1 or 2. There were no clinically meaningful differences across treatment groups. One subject in the secukinumab Q4W group and one subject in the placebo group had grade 3 abnormalities in haemoglobin (<80 g/L); grade 3 decreases in neutrophil count occurred in 2 subjects (one in secukinumab Q2W and one in placebo).

Apart from the grade 3 haemoglobin abnormalities reported in Treatment Period 1, no additional subject had grade 3 anaemia in the Entire Study Period. One additional subject in the Any secukinumab Q2W group had grade 3 neutropenia and two subjects in the Any secukinumab Q4W group had grade 4 neutropenia in the Entire Study Period.

Safety data from the full 52-week dataset revealed one new grade 3 abnormality for hematology and one for clinical chemistry since the primary endpoint analysis. Overall, it is agreed that there were no clinically meaningful differences in the newly occurring or worsening hematology or clinical chemistry including liver function abnormalities across treatment groups during the Entire Study Period assessed on the full safety set. Most of these abnormalities were of grade 1 or grade 2.

Safety topics of interest

It is agreed with the MAH that, overall, the frequency of AEs categorized as compound and class-related risks, and important potential and identified risks was generally similar across treatment groups in both Treatment Period 1 and the Entire Study period, except for the SOC Infections and infestations, which had a higher EAIR in the Q2W group compared to the Q4W group, however, the EAIR in both treatment regimens was lower than in the placebo group. The cases reported for Infections and infestations (SOC) were mainly non-serious and manageable. Three subjects discontinued study treatment due to an infection: a serious event of worsening of scrotal infection was reported in 1 subject in the Any secukinumab Q4W group (severe and not suspected to be related to study treatment), vulvovaginal candidiasis in 1 subject in the secukinumab Q4W group (non-serious, severe and suspected to be related to study treatment) and large intestinal infection in 1 subject in the secukinumab Q2W group (serious event of infectious colitis, severe and suspected to be related to study treatment.

Based on the known safety profile of secukinumab, an increased risk of IBD is known to occur in patients with HS. New onset IBD was rare and reported in only 2 subjects during Treatment Period 1. One subject in the secukinumab Q2W treatment group discontinued study treatment due to an SAE of ulcerative colitis and 1 subject in the secukinumab Q4W group discontinued study treatment due to an SAE of IBD. Both cases were considered by the Investigator to be related to study treatment.

Neutropenia was also rare, and mostly grade 1 or 2 events. Grade 3 neutropenia (<1.0 - 0.5 x 10E9/L) was reported in 2 subjects (1 subject in the secukinumab Q2W group and 1 subject in the placebo group). Both subjects had baseline values within the reference range. The subject on placebo experienced grade 3 neutropenia at Week 16; this was a single event and the subject's neutrophil count returned to normal at a subsequent visit. The subject on secukinumab Q2W with grade 3 neutropenia (single event) improved to grade 2 and 1 at the subsequent visits. Both subjects completed treatment and the study. There were no grade 4 neutropenia events.

The incidence of Candida infections (HLT: including PTs of oral candidiasis, skin candida, vulvovaginal candidiasis, candida infection and balanitis candida) was low, with a similar incidence reported across all treatment groups (1.9% in the secukinumab Q2W group and 1.7% in both the secukinumab Q4W and placebo groups). The majority of these cases were non-serious and manageable.

The incidence of Fungal infectious disorder (HLGT) was slightly higher in the secukinumab Q2W group compared to the secukinumab Q4W and placebo groups (5.3% in secukinumab Q2W, 3.9% in secukinumab Q4W, 2.8% in placebo). The PTs were all muco-cutaneous events and all cases were non-serious, manageable with standard therapy and of limited duration, thus the difference did not appear clinically significant. Furthermore, all events were mild to moderate and at the time of data cut-off approximately 90% of the events that occurred in Treatment Period 1 were considered resolved and none led to study treatment discontinuation or interruption.

The safety data on the AESI from the full 52-week dataset was consistent with the results from the initial interim analysis. If differences were seen, they are considered not to have a significant impact on the already established safety profile of secukinumab. Pooled pivotal safety data from the Entire Study Period were in-line with these data.

Immunogenicity

Consistent with the trials across the approved indications for secukinumab, treatment emergent ADAs were rare (<1%) in secukinumab-treated subjects with HS, and were not associated with loss of efficacy, PK changes or AEs related to immunogenicity.

COVID-19 pandemic

According to the MAH, the COVID-19 pandemic had a substantial impact on the recruitment and the timelines of the two HS phase 3 studies. Precautions were taken (Protocol Amendment 01) to mitigate potential risk of the COVID-19 pandemic on the study, allowing for flexibility with regards to home treatment administration and increasing the study population by 15% to account for missed doses and efficacy assessments. There were 13 suspected and confirmed cases of COVID-19 reported during Treatment Period 1 (6 cases in the secukinumab Q2W group, 3 in the secukinumab Q4W group and 4 in the placebo group). The majority of these cases of COVID-19 infection were mild, all cases resolved, and none led to study discontinuation. Thus, overall, the impact of the pandemic on the safety results appears to have been minimal.

Long-term data

The long-term safety profile appeared similar to that previously reported for secukinumab (for both treatment regimens), with no new and unexpected findings. The generally favourable risk profile of secukinumab in treatment of HS is also supported by substantial experience in the post-marketing setting across the already authorised therapeutic indications.

The long-term extension study of studies M2301 and M2302 (study M2301E1) is noted, and the CHMP has recommended the MAH to submit these results for assessment once they become available. These data are not considered essential in the context of the current variation application.

Comparison of safety in psoriasis and HS

As the Q2W administration of secukinumab 300 mg has recently been approved for use in PsO patients in the EU, a comparison to available safety data from study A2324 was performed. Acknowledging the limitations of this type of comparisons, the overall safety profile of the secukinumab 300 mg Q2W regimen in HS (studies M2301 and M2302) was comparable to that of moderate to severe psoriasis (study A2324). However, an overall higher incidence of AEs and overall EAIRs of AEs was observed in HS patients. As stated by the MAH this could be related to disease specific aspects (i.e., HS population presenting higher inflammatory burden and broad spectrum of associated co-morbidities, open wounds) and supported by the higher incidence rates of PTs often reported as associated with HS (i.e., headache, worsening of hidradenitis and diarrhoea). The EAIRs of SAEs in subjects treated with secukinumab in the Entire Study Period was comparable between the HS and the psoriasis populations.

2.5.2. Conclusions on clinical safety

In conclusion, treatment of adult patients with moderate to severe HS with secukinumab, evaluated in two identical pivotal phase 3 studies (M2301 and M2302) at two different dose regimens (secukinumab 300 mg Q2W and secukinumab 300 mg Q4W) showed overall a safety profile similar to that previously established for secukinumab across various other indications, both short-term (Treatment Period 1, up to Week 16) and the longer term (Entire Study Period, up to 52 weeks). The safety results on the full safety data set were overall consistent with the results of the placebo controlled Treatment period 1 and the initial interim analysis on the subset (approx. 60%). No new or unexpected safety findings were evident.

The CHMP concluded that the safety profile of secukinumab in treatment of adult patients with moderate to severe HS is considered acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 11.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Infections and infestations Hypersensitivity
Important potential risks	Malignant or unspecified tumors Major Adverse Cardiovascular Events (MACE) Hepatitis B reactivation Suicidal ideation and behavior
Missing information	Fetal exposure in utero Long-term safety data

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
Category 3 - Required additional pharmacovigilance activities.				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
CorEvitas Psoriasis Registry Ongoing	The primary goal of the registry is to assess the incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy.	Malignant or unspecified tumors Long-term safety Suicidal ideation and behavior	Final study report submission	June-2033
CAIN457F2304E1 Secukinumab long term efficacy, safety and tolerability in JPsA and ERA up to 4 Years Ongoing	The primary objective of this study is to evaluate the long-term efficacy of subcutaneously administered secukinumab (provided as pre-filled syringes) with respect to JIA ACR30 response over time up to Week 308 visit in patients with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304.	Long-term safety	Final study report submission	27-May-2025

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified Risks		
Infections and infestations	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** No risk minimization measures	None.
Hypersensitivity	**Routine risk minimization measures** SmPC Section 4.3, 4.4, 4.8 **Additional risk minimization measures** No risk minimization measures	None.
Important Potential Risks		

Safety concern	Risk minimization measures	Pharmacovigilance activities
Malignant or unspecified tumors	None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy; estimated sample size 3000, follow up period of 8 years
Major Adverse Cardiovascular Events (MACE)	None.	None.
Hepatitis B reactivation	None.	None.
Suicidal ideation and behavior	None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to severe psoriasis patients (including PsA) on secukinumab therapy will also be utilized to assess long-term safety, including SIB; estimated sample size 3000, follow up period of 8 years.
Missing Information		
Fetal exposure in utero	**Routine risk minimization measures** SmPC Section 4.6 **Additional risk minimization measures** No risk minimization measures	None.
Long-term safety data	None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Registry to assess incidence and nature of malignancies in a real-world population of moderate-to-severe psoriasis patients (including PsA patients) on secukinumab therapy; estimated sample size 3000, follow up period of 8 years. A study to evaluate the long-term efficacy of subcutaneously administered secukinumab (provided as pre-filled syringes) with respect to JIA ACR30 response over time up to Week 308 visit in patients with active JPsA and ERA subtypes of JIA and who completed the Phase III study CAIN457F2304.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- A full user test was carried for the original application of Cosentyx (secukinumab) in the indication of plaque psoriasis, and two additional full user tests of the Cosentyx PL were performed during the registration of the psoriatic arthritis (PsA) and ankylosing spondylitis (AS) indications.
- The previously approved Cosentyx PL has now been updated with information related to the new proposed indication of moderate to severe Hidradenitis Suppurativa (HS). The changes proposed to be included in the Cosentyx PL are minor and limited to the following:
    - the indication wording, which is in line with the wording for the compound already approved for the HS indication in Europe (Humira/adalimumab),
    - the posology wording, which is already approved for the psoriasis indication.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HS is a painful, chronic, recurrent, and debilitating inflammatory skin condition of the pilosebaceous follicle with an underlying immune system imbalance that occurs in genetically predisposed individuals. HS typically presents with painful, deep, inflammatory lesions, mostly inflammatory nodules, and abscesses, which progressively scar and suppurate and lead to malodorous discharge in the apocrine gland-bearing parts of the body. Inflammatory lesions are complicated during disease progression by sinus tract formation and fistulisation and may lead to hypertrophic scarring with a possible impact on function. The most common areas affected are the axillae, the groin and the anogenital region. HS has a highly negative impact on QoL and devastating psychological effects, with an impact greater than for many other dermatologic diseases. Patients with HS also often suffer from depression, social isolation, impaired sexual health, and difficulty performing work duties. The disease starts after puberty, and women are more frequently affected than men in a ratio of 3:1. Risk factors include obesity and smoking. Although epidemiological prevalence estimates vary widely (0.03% to 4.0%) and geographical differences exist, a prevalence of approximately 0.1% to 1% is accepted by the scientific community.

3.1.2. Available therapies and unmet medical need

Current treatment guidelines recommend a variety of medical treatments that can be used to manage the disease, including topical and systemic antibiotics, hormonal therapies, retinoids, systemic immunomodulators and biologics. Recurrent combination therapy using multiple antimicrobials represents the first step to control the symptoms in patients with HS. However, it is recognised that HS is not an infectious disease, but rather a chronic inflammatory condition, with elevated systemic levels of inflammatory markers. Therefore, systemic anti-inflammatory agents are a more appropriate therapeutic strategy than antibiotics. Once irreversible fibrosis occurs, medical treatment can only control some symptoms, while the only option to manage fibrotic lesions is surgery. Currently, adalimumab (Humira), an anti-TNF-α antibody, is the only biologic therapy approved for the treatment of adults with moderate to severe HS (approval granted in 2015 in the US and EU). Two similarly designed Phase 3 studies

demonstrated the superiority of weekly adalimumab over placebo with respect to Hidradenitis Suppurativa Clinical Response (HiSCR) rate at Week 12: 41.8% adalimumab vs. 26.0% placebo in PIONEER I, and 58.9% adalimumab vs. 27.6% placebo in PIONEER II. However, considering the very limited treatment armamentarium, an unmet need exists for additional systemic therapies.

3.1.3. Main clinical studies

The variation application is supported by two identical double-blind placebo-controlled studies with two secukinumab regimens (identical loading with 300 mg at weeks 0, 1, 2, 3 and 4, followed by a maintenance regimen of either 300 mg Q2W or 300 mg Q4W). The duration of the placebo-controlled period was 16 weeks, and it was followed by a 36-week double-blind period for which all subjects on placebo until Week 16 were switched to one of the secukinumab regimens. The primary endpoint was HiSCR50 response at Week 16; secondary multiplicity-controlled endpoints at Week 16 were abscess and nodule (AN) count, occurrence of flares, and NRS30 response for pain.

Within the initial submission, long-term Week 52 efficacy and safety data were provided for approximately 60% of subjects who had completed 52 weeks of treatment at the time of the primary endpoint analysis data cut-off dates for the submission. With the responses to the 1st RSI, the MAH provided additional analyses based on the full 52-week data and within the response to the 2nd RSI the overall pooled safety data for the two pivotal studies.

3.2. Favourable effects

In both studies, the proportion of subjects with a HiSCR50 response at Week 16 was higher in both secukinumab groups compared to placebo, and favourable effects were also consistently seen on the secondary endpoints. Some variability was seen between the two studies; notably, in study M2302, the Q4W regimen outperformed the Q2W regimen e.g., on HiSCR50. In pooled data, the magnitudes of the treatment effects with Q2W and Q4W were overall very similar.

For HiSCR50 response at Week 16, the results were as follows:

- M2301:
    - Q2W vs placebo: 45.0% vs. 33.7%, OR 1.75 (95% CI 1.12, 2.73), p=.0070
    - Q4W vs placebo: 41.8% vs. 33.7%, OR 1.48 (0.95, 2.32), p=.0418
- M2302:
    - Q2W vs placebo: 42.3% vs. 31.2%, OR 1.64 (1.05, 2.55), p=.0149
    - Q4W vs placebo: 46.1% vs. 31.2%, OR 1.90 (1.22, 2.96), p=.0022
- Pooled data:
    - Q2W vs placebo: 43.7% vs. 32.4%, OR 1.69 (1.24, 2.31), p=.0005
    - Q4W vs placebo: 43.9% vs. 32.4%, OR 1.67 (1.22, 2.29), p=.0007

For percentage reduction in AN count from baseline to Week 16, the results were as follows:

- M2301:
    - Q2W vs placebo: -46.8 vs. -24.3, LS mean diff (SE) -23.05 (-33.90, -12.21), p <.0001
    - Q4W vs placebo: -42.4 vs. -24.3, LS mean diff -18.46 (-29.32, -7.60), p=.0004

- M2302:
    - Q2W vs placebo: -39.3 vs. -22.4, LS mean diff -16.33 (-28.79, -3.88), p=.0051
    - Q4W vs placebo: -45.5 vs. -22.4, LS mean diff -22.94 (-35.24, -10.63), p=.0001
- Pooled data:
    - Q2W vs placebo: -43.1 vs. -23.3, LS mean diff -19.98 (-28.27, -11.69), p<.0001
    - Q4W vs placebo: -44.0 vs. -23.3, LS mean diff -20.82 (-29.02, -12.62), p<.0001

For cumulative flare rate at Week 16, the results were as follows:

- M2301:
    - Q2W vs placebo: 15.4% vs. 29.0%, OR 0.42 (95% CI 0.25, 0.73), p=.0010
    - Q4W vs placebo: 23.2% vs. 29.0%, OR 0.71 (0.43, 1.17), p=.0926
- M2302:
    - Q2W vs placebo: 20.1% vs. 27.0%, OR 0.68 (0.41, 1.14), p=.0732
    - Q4W vs placebo: 15.6% vs. 27.0%, OR 0.49 (0.29, 0.84), p=.0049
- Pooled data:
    - Q2W vs placebo: 17.7% vs. 28.0%, OR 0.54 (0.37, 0.77), p=.0005
    - Q4W vs placebo: 19.4% vs. 28.0%, OR 0.60 (0.42, 0.87), p=.0032

For pain (NRS30 response among subjects with a NRS score of 3 or higher, formally analysed only for pooled data), the results were as follows:

- Pooled data:
    - Q2W vs placebo: 36.6% vs. 23.0%, OR 2.08 (95% CI 1.37, 3.16), p=.0003
    - Q4W vs placebo: 33.5% vs. 23.0%, OR 1.77 (1.15, 2.70), p=.0044
- M2301:
    - Q2W vs placebo: 34.1% vs. 23.8%, OR 1.84 (1.00, 3.40)
    - Q4W vs placebo: 32.2% vs. 23.8%, OR 1.67 (0.89, 3.15)
- M2302:
    - Q2W vs placebo: 38.6% vs. 22.4%, OR 2.29 (1.28, 4.09)
    - Q4W vs placebo: 34.7% vs. 22.4%, OR 1.86 (1.03, 3.37)

Based on observed data:

- HiSCR50 response rate at Week 52 for the secukinumab Q2W and Q4W dose regimens was 52.3% and 47.1% in M2301, and 65.0% and 62.2% in M2302, respectively.
- Mean percentage change in AN count from baseline to Week 52 with the secukinumab Q2W and Q4W dose regimens was −59.9% and −54.9% in M2301, and −56.3% and −61.1% in M2302, respectively.

In the pooled data for M2301 and M2302, NRS30 response rates at Week 52 were 55.2% and 53.0% for Q2W and Q4W, respectively (NRS30 response was reported for subjects with a baseline NRS score ≥3).

3.3. Uncertainties and limitations about favourable effects

The principal initial concern was related to the MAH's choice regarding the recommended posology. Although the results do not show any consistent benefit of the Q2W regimen over the Q4W regimen, the MAH initially proposed that all HS patients be maintained on a Q2W regimen, as opposed to the Q4W regimen that is used across all other authorised indications. While the theoretical grounds for HS patients potentially requiring slightly higher doses are acknowledged, the benefit of the Q2W maintenance regimen over Q4W was considered minimal and unconvincingly demonstrated. Posologies permitting escalation based on clinical response are already authorised for the plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis indications, and although escalation strategies were not directly pursued within the current programme, the MAH was requested to justify the benefit of starting with Q2W dosing instead of starting with Q4W dosing with the option to titrate to Q2W dosing on the basis of treatment response. The MAH agreed to amend the posology accordingly, and the issue is thereby considered resolved.

Results for Week 52 data are mostly based on observed data, and some inherent biases are thus unavoidable. Nevertheless, considering the descriptive nature of the long-term data, it is considered that maintenance of effect has been sufficiently demonstrated.

More long term data will be provided with the ongoing extension study M2301E1. The study evaluates the effect of treatment interruption (randomised withdrawal) and re-treatment with secukinumab on efficacy, tolerability and safety in subjects with moderate to severe HS who completed either of the two Phase 3 studies, M2301 or M2302. The CHMP recommends the MAH to submit these results for assessment once they become available.

3.4. Unfavourable effects

During *Treatment Period 1* (up to 16 weeks; placebo control), the overall incidence of AEs was similar between the secukinumab treatment groups (65.1% and 64.4% in the secukinumab Q2W and Q4W groups, respectively) and the placebo group (65.0%). No meaningful differences in AE frequency or clinical relevance were reported between the secukinumab Q2W and Q4W groups. AEs were mostly non-serious (approximately 98%), mild to moderate in severity (approximately 97%), and did not require drug discontinuation (approximately 99%).

The AEs with the highest frequency were reported in the SOC of Infections and infestations, with similar incidences across the secukinumab groups (30.7% vs. 30.6% in the secukinumab Q2W and Q4W groups, respectively) and placebo group (31.7%), with the most commonly reported AEs being headache (10.4%), nasopharyngitis (8.0%) and (worsening of) hidradenitis (5.1%). No deaths were reported. The incidence of SAEs was low and comparable for both secukinumab regimens and placebo (2.5% for both secukinumab Q2W and secukinumab Q4W versus 3.0% for placebo), with the most commonly reported SAEs in the SOC Infections and infestations. No pattern in the type of event was evident.

During the 52-week *Entire Study Period*, in analysis of the initial subset (approx. 60%) of patients, (from week 16 onward all patient receiving secukinumab), after adjusting for exposure, the overall incidence of AEs was lower in the Any secukinumab group than the placebo group (285.2 vs. 412.2 per 100 subject-years). The EAIR rate was lower for the secukinumab Q2W group compared to the secukinumab Q4W group (274.3 vs. 296.7 per 100 subject-years) and for the Any secukinumab Q2W group compared to the Any secukinumab Q4W group (266.4 vs. 306.0 per 100 subject-years).

The SOC with the highest EAIR in the Any secukinumab group was Infections and infestations. A higher incidence was reported in the Any secukinumab Q2W group compared to the Any secukinumab Q4W group (92.5 vs. 84.1 per 100 subject-years), with the most reported PT being nasopharyngitis. No differences were observed in the EAIRs of other SOCs between the secukinumab dose regimens.

Long term data

The most commonly reported (≥10 per 100 subject-years) AEs by PT in the Any secukinumab group were headache (20.9 per 100 subject-years), (worsening of) hidradenitis and nasopharyngitis (both 14.8 per 100 subject-years). No meaningful differences in AE frequency or clinical relevance were reported between the secukinumab Q2W and Q4W groups, with the majority (approximately 98%) of the reported AEs being non-serious, mild to moderate in severity (approximately 97%) not requiring drug discontinuation (approximately 99%). In the Entire Study Period, the incidence of SAEs was low and comparable for both secukinumab groups (7.6% in Any secukinumab Q2W, 7.5% in Any secukinumab Q4W) with no pattern in the type of events reported. The two deaths reported were considered unrelated to the study drug.

The initially pending long-term safety data (approximately 40 %) from the two pivotal phase 3 HS studies was subsequently provided, as requested. The results from the assessment of these submitted full 52-week long-term safety data of secukinumab in the treatment of HS are, overall, in line with the results of the initial interim (approx. 60%) results.

3.5. Uncertainties and limitations about unfavourable effects

On request, the MAH provided updates on the full pooled 52-week data (Safety set). No further safety concerns remain. Treatment of adult patients with moderate to severe HS with secukinumab, evaluated in two identical pivotal phase 3 studies (M2301 and M2302) at two different dose regimens (secukinumab 300 mg Q2W and secukinumab 300 mg Q4W) showed overall a safety profile similar to that previously established for secukinumab across various other indications, both short-term (Treatment Period 1, up to Week 16) and the longer term (Entire Study Period, up to 52 weeks). In addition, the CHMP has recommended the MAH to submit the results of the long-term extension study M2301E1 that will provide additional long-term data.

3.6. Effects Table

Table 41 Effects Table for Cosentyx in treatment of Hidradenitis Suppurativa (data cut-off: week 16)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Clinical response	HiSRC50 response rate at Week 16 (PEP)	%	Q2W: 45.0 Q4W: 41.8	33.7		M2301
			Q2W: 42.3 Q4W: 46.1	31.2		M2302
			Q2W: 43.7 Q4W: 43.9	32.4		Pooled
Flares	Flare rate at Week 16	%	Q2W: 15.4 Q4W: 23.2	29.0		M2301
			Q2W: 20.1 Q4W: 15.6	27.0		M2302
			Q2W: 17.7 Q4W: 19.4	28.0		Pooled
Reduction in pain	NRS30 response rate at Week 16	%	Q2W: 36.6 Q4W: 33.5	23.0	Analysed among subset with baseline NRS 3 or higher	Pooled

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Up to week 16 (placebo controlled) Pooled M2301 and M2302 (Safety set)						
All TEAEs	Pooled M2301 and M2302 safety data	%	Q2W: 65.1 Q4W: 64.4	65.0	Mostly non-serious (approx. 98%), mild to moderate in severity (approx. 97%) and did not require drug discontinuation (approx. 99%).	
Headache		%	Q2W: 10.5 Q4W: 10.3	8.0		
Nasopharyngitis		%	Q2W: 9.1 Q4W: 6.9	8.0		
Hidradenitis		%	Q2W: 5.8 Q4W: 4.4	10.5		
Diarrhoea		%	Q2W: 3.6 Q4W: 5.6	6.1		
All SAEs		%	Q2W: 2.5 Q4W: 2.5	3.0		
Infections and Infestations SOC		%	Q2W: 30.7 Q4W: 30.6	31.7	Generally mild to moderate in severity and resolved	
Candida Infections (HTL)		%	Q2W: 1.9 Q4W: 1.7	1.7	No cases of oesophageal or other invasive candida infection	
Fungal infections (HLGT)		%	Q2W: 5.3 Q4W: 3.9	2.8	All muco-cutaneous, non-serious, non-severe and did not lead to discontinuation; were manageable with standard therapy.	
Serious infection		n	Q2W: 1 Q4W: 4	3		
Hepatitis B reactivation		n	Q2W: 0 Q4W: 0	0		
Covid-19		n	Q2W: 6 Q4W: 3	4	Mostly mild, all resolved	
Hypersensitivity		%	Q2W: 5.3 Q4W: 3.9	4.4	None were serious, no anaphylactic reactions	
Malignant and unspecified tumours		%	Q2W: 0 Q4W: 0.6	0.6		
Any neutropenia TEAE		n	Q2W: 1 Q4W: 0	1	Mostly grade 1 and 2, single events and transient.	
MACE		n	Q2W: 0 Q4W: 0	0		
IBD		n	Q2W: 1 Q4W: 1	0		
Suicidal ideation and behaviour		%	Q2W: 0.3 Q4W: 0.3	0		
Deaths		n	Q2W: 0 Q4W: 0	0		
Long term data up to week 52						
The long-term safety data of the *Entire Study Period* of 52 weeks were in line with the safety						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
profile of the placebo controlled 16 week *Treatment period 1*. No new or unexpected safety signals for secukinumab in treatment of HS were detected.						

Abbreviations: HiSCR = Hidradenitis suppurativa clinical response; NRS = Numerical Rating Scale; PEP = primary endpoint; Q2W = every two weeks; Q4W = every four weeks. PT, Preferred term; HLT, Higher level term; HLGT, higher level group term.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Primary assessment of efficacy was based on the HiSCR50 response rate, which has been previously used as the basis of authorisation for adalimumab in HS; the use of HiSCR50 was also endorsed by the CHMP in a Scientific Advice procedure. Based on pooled data from the two studies, the HiSCR50 response rate at Week 16 was about 11 percentage points higher than for placebo with either of the secukinumab maintenance regimens. Despite the identical designs, some differences were observed between the two studies: in M2301, the difference in response rates between the Q2W and Q4W regimens was 3 percentage points, and in M2302, the treatment difference vs. placebo was numerically larger for the Q4W regimen than the Q2W regimen.

The magnitude of the treatment effect observed with secukinumab is considered of clinical relevance by the CHMP. Due to differences between secukinumab studies and the registrational studies with adalimumab it is not possible to directly compare their results, however secukinumab offers an alternative treatment for patients with HS.

Results on secondary endpoints (reduction in abscess and inflammatory nodule count, flares, and pain) were consistent with the HiSCR response and can be viewed as further supporting a clinically relevant effect of secukinumab on the symptoms and manifestations of HS. Long-term data from the 52-week dataset supports adequate maintenance of effect.

No added benefit could be demonstrated for a Q2W regimen compared to a Q4W regimen, therefore at the CHMP request the MAH proposed an escalation strategy in patients with an insufficient response, similar to that already authorised for several other indications for Cosentyx.

With respect to the proposed indication, it is noted that consistent effects were seen between Hurley stages II and III; it is thereby agreed that the indication can cover patients with moderate to severe HS. It is understood that the proposed indication "moderate to severe" is likely to be interpreted as referring to Hurley stages II and III and can thereby be justified. In addition the MAH agreed to update the indication to mention "active" in it, as a qualifier for disease state. The indication is therefore acceptable for the CHMP.

Currently, after assessment of the short term and long-term safety data, the safety profile of secukinumab in the treatment of moderate to severe HS appears favourable.

No new or unexpected safety signals were evident. The generally favourable risk profile is also supported by substantial experience in the post-marketing setting across the already authorised therapeutic indications.

The long-term extension study of studies M2301 and M2302 (M2301E1) is noted, the CHMP recommends the MAH to submit these results for assessment once they become available. Data from the extension study are not considered essential in the context of the current variation application.

3.7.2. Balance of benefits and risks

The treatment effect for secukinumab in HS, as regards data at Week 16, can be considered adequately demonstrated, and while it is of quite modest magnitude, it can be considered clinically relevant, particularly when contextualised with the dearth of currently available therapies for this difficult disease. The clinical relevance is supported by safety data that is in line with the favourable profile observed in previous studies in other conditions as well as post-marketing experience. Long-term data from the HS studies support maintenance of effect as well as an acceptable safety profile until Week 52.

3.8. Conclusions

The overall B/R of Cosentyx is positive in the following indication:

Hidradenitis suppurativa (HS)

Cosentyx is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy (see section 5.1).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of Hidradenitis Suppurativa (HS) for cosentyx, based on results from two Phase 3 studies CAIN457M2301 (SUNSHINE) and CAIN457M2302 (SUNRISE). These studies are multi-center, randomized, double-blind, placebo-controlled, parallel group Phase 3 studies conducted to assess the short (16 weeks) and long-term (up to 52 weeks) efficacy and safety of two secukinumab dose regimens (Q2W or Q4W) compared to placebo in adult subjects with moderate to severe HS. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.1 of the RMP has also been approved.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Cosentyx-H-C-003729-II-0090'

Attachments

1. SmPC Package Leaflet (changes highlighted) as adopted by the CHMP on 26 April 2023.